Medicines & Healthcare products Regulatory Agency

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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This month we remind healthcare professionals to inform patients about the potential side effects of glucagon-like peptide-1 (GLP-1) receptor agonists. These include common gastrointestinal side effects such as nausea, diarrhoea, vomiting and constipation which may progress to more serious conditions such as severe dehydration.

We also ask healthcare professionals to support new guidance for users of diabetes management equipment, which explains how to report safety concerns to the MHRA using the Yellow Card scheme.

Healthcare professionals are also reminded of the importance of monitoring blood pressure when prescribing bromocriptine for prevention or inhibition of post-partum physiological lactation.

Finally, we provide a summary of recent letters and notifications sent to healthcare professionals about medicines and medical devices.

If you have been forwarded this issue of the Drug Safety Update, you can subscribe directly via our website.

GLP-1 receptor agonists: reminder of the potential side effects and to be aware of the potential for misuse

Healthcare professionals are reminded to inform patients about the common and serious side effects associated with glucagon-like peptide-1 receptor agonists (GLP-1RAs).

Advice for healthcare professionals:

- inform patients upon initial prescription and when increasing the dose about the common risk of gastrointestinal side effects which may affect more than 1 in 10 patients. These are usually non-serious, however can sometimes lead to more serious complications such as severe dehydration, resulting in hospitalisation
- be aware that hypoglycaemia can occur in non-diabetic patients using some GLP-1RAs for weight management; ensure patients are aware of the symptoms and signs of hypoglycaemia and know to urgently seek medical advice should they occur
- patients should also be warned of the risk of falsified GLP-1 RA medicines for weight loss if not prescribed by a registered healthcare professional, and be aware that some falsified medicines have been found to contain insulin[1]
- be aware there have been reports of potential misuse of GLP-1RAs for unauthorised indications such as aesthetic weight loss
- report suspected adverse drug reactions to the Yellow Card scheme

Advice for healthcare professionals to provide to patients:

- GLP-1RAs are prescription-only medicines to be used under medical supervision and should only be prescribed by a registered healthcare professional
- the benefits and risks of using a GLP-1RAs for weight loss outside of the licensed indications have not been studied
- common gastrointestinal side-effects of GLP-1RAs treatment (including nausea, vomiting, diarrhoea and constipation) can persist for several days and may affect more than 1 in 10 patients. This may result in dehydration, which if severe may lead to other serious health complications such as kidney damage resulting in hospitalisation
- throughout treatment stay well hydrated by drinking plenty of fluids (such as water) to avoid dehydration, which can sometimes occur after experiencing gastrointestinal side-effects including vomiting and diarrhoea
- other serious but less common side-effects of GLP-1RAs include acute gallstone disease, pancreatitis, and serious allergic reactions
- if obtaining a private prescription (from a non-NHS prescriber), ensure that this is dispensed from authorised sources, such as registered online pharmacies, to avoid the risk of receiving falsified pens
- carefully read the instructions for use in the Patient Information Leaflet, and use the prescribed dose
- if you are concerned about any side-effects, speak to a healthcare professional

Background

GLP-1RAs are effective and acceptably safe treatments when used within their licensed indications. However, as with all medicines, there are risks associated with their use.

GLP-1RAs are a class of medications used to treat type II diabetes mellitus and obesity. Five GLP-1RAs are available in the UK: dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide. Wegovy, which contains semaglutide, is also licensed as a preventative treatment to reduce the risk of cardiovascular events in patients with established cardiovascular disease. Mounjaro (tirzepatide) is a GLP-1RA combined with glucose-dependent insulinotropic polypeptide receptor agonist (GIP RA).

Some of the GLP-1RA products have more than one brand name and more than one indication. Annex 1 lists the GLP-1RA products currently authorised in the UK with their brand names and indications.

Public interest in the use of GLP-1RA products for weight loss is high. GLP-1RA products licensed for weight reduction are effective treatment options for patients who have obesity (with a BMI above 30kg/m^2) or who are overweight with weight-related comorbidities (with a BMI above 27kg/m^2) such as cardiovascular disease. Saxenda (liraglutide), Wegovy (semaglutide) and Mounjaro (tirzepatide) are the only GLP-1RA products licensed for weight management.

There has been anecdotal evidence and adverse drug reaction reports suggesting misuse of GLP-1RA products for weight management by individuals outside of the licensed indication. The benefits and risks of using these medicines for weight loss by individuals who do not have obesity or who are not overweight with weight-related comorbidities have not been studied.

Risk of adverse drug reactions associated with GLP-1RA medicines

To ensure informed decision-making when prescribing GLP-1RAs for weight management, it is important that patients are aware of the potential adverse drug reactions associated with these medicines. These include common gastrointestinal reactions, that, if not managed effectively, can lead to serious complications.

Gastrointestinal side effects are more likely to occur at the start of treatment or after a recent increase in dose. Healthcare professionals should also discuss the serious, but less common risks such as pancreatitis and gall bladder disorders which may occur in between 1 in 100 and 1 in 10,000 patients dependent on the GLP-1RA.

The risk of hypoglycaemia in non-diabetic patients is included in the product information for Saxenda and Wegovy which are licensed for weight management; patients should be made aware of the signs and symptoms of hypoglycaemia and what action to take.

The MHRA has received Yellow Card reports for individuals who have been hospitalised due to suspected adverse drug reactions with GLP-1RAs when used for weight loss. Severe dehydration following gastrointestinal adverse drug reactions has been reported, including for individuals who may not meet the prescribing criteria and

may have used these medicines inappropriately for weight loss. It is, however, difficult to confirm the inappropriate use or misuse of medicines from the Yellow Card data.

As of 16 August 2024, the MHRA has received 5073 reports of common gastrointestinal reactions (including nausea, vomiting and diarrhoea) in association with GLP-1RAs indicated for weight management. Of these reports, 46 reported hospitalisation of the individual. Reports have also been received by the MHRA that do not specify a brand name or provide details about indication of use and subsequently have not been included in this data.[2]

When interpreting this information, it is important to understand that the exact number of individuals using these medicines is unknown. The lack of prescribing data makes it difficult to determine how common an adverse drug reaction is. Additionally, the number of reports can be influenced by actual usage of the medicine, availability of the medicine and length of time since it was licenced for use. Due to the limitations of spontaneous reporting, some reports may lack information on serious outcomes including hospitalisation, and reports that did not report an indication without a brand name have not been included in this data, potentially underestimating the risk. Please also note that some reports may have reported other serious adverse drug reactions which may have also been the primary cause of hospitalisation, unrelated to gastrointestinal adverse drug reactions. Reports have been received that contain more than one common gastrointestinal adverse drug reaction, for example, vomiting and nausea.

Report any suspected adverse drug reactions

Healthcare professionals should continue to report suspected adverse drug reactions to the Yellow Card scheme. When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, product brand name, details of your suspicion of inappropriate use or misuse and include all relevant patient details including weight or BMI, and if possible, where the product was obtained (i.e. NHS prescription, private prescription, including online prescriptions, or illegitimate supplier). Reporting suspected ADRs, even those known to occur, adds to knowledge about the frequency and severity of these reactions and can be used to identify patients who are most at risk. Your report helps the safer use of medicines.

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

For queries or more information, please contact info@mhra.gov.uk

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Annex

Annex 1: GLP-1RA-containing products authorised in the UK

References

1. Drug Safety Update volume 17, issue 4: November 2023: 1.: https://www.gov.uk/drug-safety-update/ozempicv-semaglutide-and-saxenda-liraglutide-vigilance-required-due-to-potentially-harmful-falsified-products

2. The data lock point for the Yellow Card reporting presented here is 16 August 2024. This data will not be updated as more Yellow Card reports are received.

Insulin pumps and continuous glucose monitoring (CGM) equipment: guidance for users on reporting suspected adverse incidents and safety concerns to the MHRA's Yellow Card scheme

We ask healthcare professionals to support new guidance for users of diabetes management equipment, their families, care givers and representatives. It explains how to report safety concerns to the MHRA using the Yellow Card scheme and describes the information we need to support our device investigations.

Advice for healthcare professionals:

- insulin pumps and continuous glucose monitoring (CGM) devices are complex devices with the potential to result in serious harm in the event of error. To aid the MHRA in early identification of safety concerns associated with these devices, users of the equipment need to know how to report safety issues to the MHRA
- we have published guidance to explain to users of all medical devices manufactured for diabetes management how to report safety concerns to the MHRA using the Yellow Card scheme
- this guidance is expected to improve the quality of information the MHRA receives and should the need arise, support a thorough investigation of the relevant equipment
- highlight the guidance to patients using insulin pumps, insulin pens and CGM devices
- remind patients that if they suspect a problem with their device, they should be advised to use an alternative method to manage their diabetes
- we are also providing a poster with a direct link to the guidance (QR code) which can be printed to display in your clinic waiting room
- healthcare professionals should also speak to their local Medical Device Safety Officer (MDSO) on how you can support the reporting of adverse incidents with these medical devices
- report problems and adverse incidents associated with medical devices used in the management of diabetes on a Yellow Card

Advice for healthcare professionals to provide to patients:

- seek medical advice without delay if you have concerns that your health has been impacted by a potential safety issue relating to your device
- use an alternative device if you suspect your current device is not performing adequately in managing your diabetes. Ensure you have an alternative device available at all times
- it is important to read the guidance being given to you on how to report concerns with the equipment used to manage your diabetes
- it is important that you report safety concerns with your devices to the Yellow Card scheme. Yellow Card reports help the MHRA to identify safety issues and to consider actions to improve the safety and performance of devices used by people living with diabetes

- if you believe there is a safety problem with your equipment, submit a report via the Yellow Card scheme and use the guidance document to help you create a report

Background

The MHRA has identified an opportunity to improve the number and quality of reports we receive from members of the public using insulin pumps and CGM equipment for management of their diabetes.

A lack of detail in reports received from device users has made it difficult to thoroughly investigate potential safety issues. Discussion with external stakeholders also highlighted significant under-reporting amongst users of these devices. Contributing factors to under-reporting were a lack of awareness that Yellow Card reporting can be used for medical device-related safety issues, and lack of clarity on why the issue would need to be reported twice (once to the manufacturer to request replacement units and again to the MHRA for signal detection activities).

To address the issues affecting incident reporting with these devices, we have published guidance aimed specifically at device users and their families, care givers and representatives on why reporting concerns to us is important, what information they should include, and step-by-step instructions on how to create a report.

The MHRA requests that healthcare professionals bring this guidance to the attention of patients using insulin pumps and CGM devices.

Reporting concerns with medical devices on a Yellow Card

If a patient tells you of problems with their equipment, please advise them to submit a report to the MHRA via the Yellow Card scheme and share the guidance document to help them.

If the patient is unable to submit a report, healthcare professionals should report incidents involving medical devices:

- in England and Wales to the Yellow Card scheme or via the Yellow Card app
- in Scotland to Incident Reporting & Investigation Centre (IRIC) and their local incident recording system
- in Northern Ireland to the Northern Ireland Adverse Incident Centre and their local incident recording system.

For queries or more information, please contact info@mhra.gov.uk

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Bromocriptine: monitor blood pressure when prescribing bromocriptine for prevention or inhibition of post-partum physiological lactation

A safety review has been conducted by the MHRA following a Yellow Card report concerning a patient who was taking bromocriptine. The review concluded that blood pressure monitoring of patients prescribed with this drug is essential especially during the first days of treatment.

Advice for healthcare professionals:

- bromocriptine should only be prescribed to suppress post-partum physiological lactation, where it is medically indicated such as intrapartum loss, neonatal death, or in some cases of HIV infection of the mother
- bromocriptine should not be used for routine lactation suppression, or for relieving symptoms of postpartum breast pain and engorgement, which can be adequately treated with non-pharmacological interventions (such as firm breast support, ice application) and simple analgesics
- use is contraindicated for patients with uncontrolled hypertension, hypertensive disorders of pregnancy (including eclampsia, pre-eclampsia or pregnancy-induced hypertension), hypertension post-partum and in the puerperium, a history of coronary artery disease or other severe cardiovascular conditions
- particular caution is required in patients who are on concomitant therapy or recent treatment with drugs that can alter blood pressure
- when prescribing bromocriptine for any of its indications, carefully monitor for an increase in blood pressure, especially during the first days of therapy and with any subsequent dose increases
- if patients prescribed bromocriptine present with signs and symptoms of hypertension, treatment should be discontinued, and the patient evaluated promptly by healthcare professionals
- clinical guidance[1] recommends cabergoline as the preferred drug for prevention or inhibition of post-partum physiological lactation, owing to the single dose regime and lower rates of rebound breast activity and adverse events. However, blood pressure monitoring is still necessary when taking cabergoline as both cabergoline and bromocriptine are dopamine agonists and should not be given to women with hypertension or pre-eclampsia
- healthcare professionals are encouraged to read the Summary of Product Characteristics (SmPC) for special warnings and contraindications for the use of bromocriptine and cabergoline
- report suspected adverse drug reactions to bromocriptine or cabergoline to the Yellow Card scheme

Advice for healthcare professionals to provide to patients:

- bromocriptine is used to prevent or stop milk production after childbirth in women who are not breastfeeding only if there are medical reasons for doing so, for

example to avoid further distress in women who lose a baby during or just after birth, or in some cases of HIV infection of the mother

- inform your doctor if you had blood pressure problems before or during pregnancy or after giving birth, such as eclampsia, pre-eclampsia, pregnancy-induced high blood pressure or high blood pressure after giving birth
- your doctor will need to check your blood pressure regularly during the first few days of treatment with bromocriptine
- seek urgent medical attention if you experience symptoms of high blood pressure, for example chest pain or unusually severe or persistent headache, with or without vision problems while taking bromocriptine
- report suspected adverse drug reactions to the Yellow Card scheme

Background

The MHRA has received a Yellow Card report which highlighted the need for blood pressure monitoring during bromocriptine treatment, especially during the first days of therapy. It is imperative that signs and symptoms of hypertension are recognised in patients receiving bromocriptine. Treatment with bromocriptine should be discontinued in hypertensive patients or when signs and symptoms of hypertension are detected and the patient promptly evaluated with consideration given as to whether they should be referred for further investigation and management of high blood pressure or close monitoring.

Bromocriptine is a dopamine agonist which inhibits the release of prolactin by the pituitary gland and induces a cyclic and physiologic oestrogen secretion. Bromocriptine is indicated for the prevention or suppression of post-partum physiological lactation only where medically indicated (such as in case of intrapartum loss, neonatal death or in some cases of HIV infection of the mother).

Bromocriptine is not recommended for the routine suppression of lactation or for the relief of symptoms of post-partum pain and engorgement which can be adequately treated with non-pharmacological interventions (such as firm breast support, ice application) and simple analgesics.

Other indications for bromocriptine include hyperprolactinaemia, menstrual cycle disorders and female infertility, premenstrual symptoms and benign breast disease, prolactinomas, acromegaly and Parkinson's disease. Blood pressure monitoring is required when bromocriptine is used for any of its indications.

Clinical Guidelines

The Royal College of Obstetricians and Gynaecologists' Guidance on Late Intrauterine Fetal Death and Stillbirth[1], Section 7.3, refers to use of both bromocriptine and cabergoline for lactation suppression but recommends cabergoline, as the single dose regime is easier to use and has shown significantly lower rates of rebound breast activity and adverse events.

Blood pressure should be carefully monitored during treatment with either bromocriptine or cabergoline, and use of these medications is contraindicated in patients with existing high blood pressure.

The Summary of Product Characteristics (SmPC) for both bromocriptine and cabergoline details the indications, contraindications as well as the precautionary warnings of blood pressure monitoring.

Reporting Advice

Please report any suspected adverse drug reactions through 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 suspected adverse drug reactions, please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, and treatment dates.

For queries or more information, please contact info@mhra.gov.uk

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References

1. Royal College of Obstetricians and Gynaecologists (RCOG) guidance on Late Intrauterine Fetal Death and Stillbirth; gtg_55.pdf (rcog.org.uk)

Letters and medicine recalls sent to healthcare professionals in September 2024

A summary of recent letters and notifications sent to healthcare professionals about medicines and medical devices.

Letters

In September 2024, the following letters were sent or provided to relevant healthcare professionals:

- Oxbryta (voxelotor): Withdrawal from UK market
- BLENREP▼ (Belantamab mafodotin): Revocation of the Great Britain conditional Marketing Authorisation for BLENREP (belantamab mafodotin)
- Valproate - containing medicines▼: new measures regarding the potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception
- Tyenne 162 mg solution for injection in pre-filled pen (PFS) - PLGB 08828/0357: Temporary Supply of German labelled stock
- NOXAFIL® (posaconazole) new Gastro-Resistant Powder and Solvent for Oral Suspension not interchangeable with existing Oral Suspension including generics.
- Fresenius Kabi compounded parenteral nutrition products: use of Inline filters during administration now required
- Creon® Micro Pancreatin 60.12mg Gastro-resistant Granules: Interim Supply of Spanish Stock to Mitigate Supply Disruption

Medicine Recalls and Notifications

In September 2024, recalls and notifications for medicines were issued on:

Class 3 Medicines Recall: Theramex HQ UK Ltd, Evorel Sequi, EL (24)A/41. Issued 12 September 2024. Theramex has informed the MHRA that some cartons of Evorel Sequi contain the incorrect combination of patches. An error at the packaging site means that a limited number of packs have the incorrect combination of Evorel 50 and Evorel Conti patches.

Class 3 Medicines Recall: Orion Pharma (UK) Ltd, Eldepryl 5mg Tablets (selegiline), EL(24)A/42. Issued 18 September 2024. Orion Pharma (UK) Ltd is recalling this batch as a precautionary measure due to an out of specification result in the assay result during the follow up stability study of the batch.

Class 4 Medicines Defect Information: Sandoz Ltd., Risperidone 1mg, 2mg, 3mg Tablets, EL(24)A/43. Issued 26 September 2024. Sandoz Ltd. has informed the MHRA that there

is missing safety information in the Patient Information Leaflet (PIL) and Summary of Product Characteristics (SmPC) for Risperidone 1mg, 2mg and 3mg and Tablets.

Class 2 Medicines Recall: Pfizer Limited, Oxbryta 500mg Tablets (voxelotor), EL(24)A/44. Issued 30 September 2024. Pfizer Limited is recalling all distributed batches of Oxbryta 500 mg Tablets. Pfizer Limited has informed the MHRA that the product is being withdrawn due to emerging data from clinical trials and registry-based studies.

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