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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In our first article, we advise that decreased vitamin B12 levels is now considered to be common with metformin treatment, especially in patients receiving a higher dose or longer treatment duration and in those with existing risk factors. We are now advising that vitamin B12 serum levels are checked in patients being treated with metformin who have symptoms suggestive of vitamin B12 deficiency and periodic monitoring considered for patients with risk factors for vitamin B12 deficiency.

In our second article, we highlight a recent safety action for Roche Accu-Chek Insight insulin pumps following reports of insulin leakage from the pre-filled cartridges and associated serious cases of hyperglycaemia and diabetic ketoacidosis. Note the actions required of the healthcare system to inform patients who use the Accu-Chek Insight insulin pump of the risks and move patients to alternative insulin pumps where possible.

On page 9, we summarise recent advice relating to COVID-19 vaccines and medicines published since the May 2022 issue of Drug Safety Update. And on page 11, we include recent letters, recalls, and notifications sent to healthcare professionals about medicines and medical devices.

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Metformin and reduced vitamin B12 levels: new advice for monitoring patients at risk

Decreased vitamin B12 levels, or vitamin B12 deficiency, is now considered to be a common side effect in patients on metformin treatment, especially in those receiving a higher dose or longer treatment duration and in those with existing risk factors. We are therefore advising checking vitamin B12 serum levels in patients being treated with metformin who have symptoms suggestive of vitamin B12 deficiency. We also advise that periodic monitoring for patients with risk factors for vitamin B12 deficiency should be considered.

Advice for healthcare professionals:

- metformin can commonly reduce vitamin B12 levels in patients, which may lead to vitamin B12 deficiency
- the risk of low vitamin B12 levels increases with higher metformin dose, longer treatment duration, and in patients with risk factors for vitamin B12 deficiency
- test vitamin B12 serum levels if deficiency is suspected (for example, in patients presenting with megaloblastic anaemia or new-onset neuropathy) and follow current clinical guidelines on investigation and management of vitamin B12 deficiency (for example, see Clinical Knowledge Summary from NICE)
- consider periodic vitamin B12 monitoring in patients with risk factors for vitamin B12 deficiency (see list of risk factors in article)
- administer corrective treatment for vitamin B12 deficiency in line with current clinical guidelines; continue metformin therapy for as long as it is tolerated and not contraindicated
- report suspected adverse drug reactions associated with metformin on a Yellow Card

Advice for healthcare professionals to give to patients or carers:

- if you are taking metformin, seek medical advice if you develop new or worsening symptoms of extreme tiredness, a sore and red tongue, pins and needles, or pale or yellow skin – these can be signs of low vitamin B12 levels
- you may need blood tests to find out the cause of your symptoms; these symptoms can also be caused by diabetes or other unrelated health issues
- you can keep taking metformin while vitamin B12 levels are being corrected
- do not stop your treatment without first discussing this with your doctor

About metformin and vitamin B12 deficiency

Metformin is a medicine authorised to treat type 2 diabetes mellitus and to help prevent type 2 diabetes in patients at high risk of developing it. Metformin is available as immediate and modified-release tablets, as well as an oral solution.

Vitamin B12 (cobalamin) is a nutrient that helps to keep the body's nerve and blood cells healthy. It is found in foods of animal origin including milk, cheese, yoghurt, and eggs. It is also added to some fortified foods such as breakfast cereals. Common causes of vitamin B12 deficiency include infections, malabsorption, medical conditions (Crohn's disease, pernicious anaemia), gastric resection, and inadequate dietary intake.

Patients with a vitamin B12 deficiency can be asymptomatic or they can present with symptoms of megaloblastic anaemia or neuropathy or both. Other symptoms of low vitamin B12 levels may include mental disturbance (depression, irritability, cognitive impairment), glossitis (swollen and inflamed tongue), mouth ulcers, and visual and motor disturbances. It is important for patients with anaemia or neuropathy caused by vitamin B12 deficiency to be diagnosed and treated as soon as possible to avoid the development of permanent symptoms.

Decreased vitamin B12 levels are a known consequence of long-term treatment with metformin. The mechanism is currently thought to be multifactorial, comprising altered intestinal motility, bacterial overgrowth, and reduced uptake of vitamin B12 within the small intestine (or a combination of these factors).

Product information update

he known adverse drug reaction of vitamin B12 deficiency was recently reviewed for the brand leader Glucophage (metformin) within Europe with input from the MHRA. After this review, we have agreed that the product information for medicines containing metformin should be updated.

The current literature suggest that the frequency of this adverse drug reaction is higher than previously thought.[1] The Glucophage product information for healthcare professionals and patients has now been updated to state that vitamin B12 deficiency is a common adverse drug reaction, and may affect up to 1 in 10 people who take it.

The product information has also been updated to note that the risk of this adverse reaction occurring increases with increasing metformin dose and treatment duration and in patients with risk factors known to cause vitamin B12 deficiency.[1,2,3,4]

The updated product information also includes new advice to healthcare professionals to test vitamin B12 levels in those presenting with anaemia or neuropathy and that periodic vitamin B12 monitoring should be considered in patients with risk factors for vitamin B12 deficiency. The product information for other medicines containing metformin will also be updated including fixed-dose combination products containing metformin.

Risk factors for vitamin B12 deficiency

Risk factors for vitamin B12 deficiency are wide ranging. They include:

- baseline vitamin B12 levels at the lower end of the normal range
- conditions associated with reduced vitamin B12 absorption (such as elderly people and those with gastrointestinal disorders such as total or partial gastrectomy, Crohn's disease and other bowel inflammatory disorders, or autoimmune conditions)
- diets with reduced sources of vitamin B12 (such as strict vegan and some vegetarian diets)
- concomitant medication known to impair vitamin B12 absorption (including proton pump inhibitors or colchicine)
- genetic predisposition to vitamin B12 deficiency, such as intrinsic factor receptor deficiency (Imerslund-Gräsbeck syndrome) and transcobalamin II deficiency

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Report suspected reactions on a Yellow Card

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

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

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

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

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

See the MHRA website for the latest information on medicines and vaccines for COVID-19.

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Footnotes

1. Aroda VR, and others. Long-term metformin use and vitamin b12 deficiency in the diabetes prevention program outcomes study. Journal of Clinical Endocrinology and Metabolism 2016; volume 101: pages 1754 to 61 (viewed on 24 April 2022).

2. Beulens JW, and others. Influence of duration and dose of metformin on cobalamin deficiency in type 2 diabetes patients using metformin. Acta Diabetologica 2015; volume 52: pages 47 to 53 (viewed on 24 April 2022).

3. de Jager J, and others. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. British Medical Journal 2010; volume 340: c2181 (viewed on 24 April 2022).

4. Miller JW. Proton Pump Inhibitors, H2-Receptor Antagonists, Metformin, and Vitamin B-12 Deficiency: Clinical Implications. Advances in Nutrition 2018; volume 9: pages 511S to 518S (viewed on 24 April 2022).

Article citation: Drug Safety Update volume 15, issue 11: June 2022: 1.

Roche Accu-Chek Insight insulin pump with NovoRapid PumpCart insulin cartridges: alert following cases of insulin leakage

We have issued a National Patient Safety Alert following serious reports of harm associated with insulin leakage during use of the Accu-Chek Insight Insulin pump with NovoRapid PumpCart prefilled insulin cartridges. Patients should be moved onto alternative insulin pumps where possible.

Advice for healthcare professionals:

- the Accu-Chek Insight Insulin pump used with NovoRapid PumpCart prefilled insulin cartridges has been associated with insulin leakage events, including cases of severe hyperglycaemia and diabetic ketoacidosis in UK patients
- follow the steps set out by your organisation to action the National Patient Safety Alert, including to identify and review patients using Roche Accu-Chek Insight insulin pumps and discuss moving them to an alternative insulin pumps where possible
- pharmacists should continue to dispense the NovoRapid PumpCart cartridges but ask patients whether they use the Accu-Chek Insight insulin pump and provide advice and education to minimise the risks (as below)
- report suspected adverse drug reactions or adverse incidents to the Yellow Card scheme

Advice for healthcare professionals to give to patients or carers:

- the MHRA has taken action following cases in which insulin has leaked from the glass cartridge in the Accu-Chek Insight insulin pump – some cases were associated with severely high blood sugar and diabetic ketoacidosis
- your healthcare professional team has been asked to discuss with you changing to another insulin pump where possible
- while you continue to use the Accu-Chek Insight Insulin pump:
    - check the pump and cartridge regularly for damages, for example cracks or leakage. If you smell insulin (a strong antiseptic chemical smell) this could also indicate a leakage.
    - follow the advice in the latest customer notice to replace previous designs for pump adaptors and tubing
    - do not use the cartridge if cracks or leakage are seen or if the cartridge was dropped. Follow the instructions of your Accu-Chek Insight user manual for replacing a cartridge and for cleaning the cartridge compartment in the insulin pump.
    - during the day and before going to sleep please carefully check that your insulin pump is delivering insulin and there are no leakages.
    - never change treatment delivery methods without first consulting a relevant healthcare professional.
    - failure of insulin delivery due to leakage may not result in an alert notification from the insulin pump and cracks and leakages may not always be visible. You should check blood glucose levels multiple times throughout your day while using pumps.
    - tell your healthcare professional immediately if you suspect a problem with your insulin delivery.

Safety issue

The Roche Accu-Chek Insight insulin pump is a medical device used by insulin-dependent patients with diabetes to deliver insulin. The Accu-Chek Insight pump is used in combination with NovoRapid PumpCart cartridges, which contain insulin (as insulin aspart) in a glass cartridge.

We have received reports of patient harm associated with leakage and over the past 3 years we have kept this safety concern under close review. In some of the reported leakage incidents, the cartridges were found to be cracked and provided an inadequate supply of insulin to patients. However, leakages also occurred in cases where no cracks in the cartridge were visible.

In some patients, serious consequences resulted from an inadequate supply of insulin. We received 25 serious cases in both 2020 and 2021 (including cases where a patient required urgent medical treatment or hospitalisation) in association with an insulin leakage event in UK patients, including 18 cases and 17 cases respectively of diabetic ketoacidosis.

Despite actions from the manufacturer to reduce the incidence of these events, we continue to receive reports of insulin leakage and we have taken further action to protect patients.

Actions for the healthcare system

Healthcare professionals should inform patients who use the Accu-Chek Insight of the risk of leakage and the updated instructions to reduce risk. Where possible, patients should be moved onto alternative pumps in accordance with the actions in the National Patient Safety Alert.

A risk assessment must be recorded with all users of Accu-Chek Insight pumps. This should involve a discussion of the risks of continuing treatment with the affected device and consider the best interest of the patient and the management of their diabetes.

Patients who continue to use the Accu-Chek Insight pump should be instructed to follow the advice in the manufacturer's latest Field Safety Notice. This includes using the new adapter and tubing. Users should also be instructed to inspect the pump and cartridges regularly for cracks or leaks, and to check blood glucose levels multiple times throughout the day. For the full recommendations to users, see the Field Safety Notice and our press release.

Roche Diabetes Care ceased marketing the Accu-Chek Insight pump in the UK at the end of 2021 and new patients will not be offered the pump. Therefore, all existing Accu-Chek Insight pump users will need to be transferred to an alternative pump at the end of their pump warranty, irrespective of the outcome of their risk assessment.

Report on a Yellow Card

Suspected adverse reactions or incidents associated with medicines or medical devices used in diabetes 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)

Please note, any medical device incidents should be reported to Health Facilities Scotland in Scotland and to the Northern Ireland Adverse Incident Centre in Northern Ireland.

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COVID-19 vaccines and medicines: updates for June 2022

Recent information relating to COVID-19 vaccines and medicines that has been published since the May 2022 issue of Drug Safety Update, up to 17 June 2022.

Product information update for Spikevax COVID-19 vaccine

We have updated the Summary of Product Characteristics for Spikevax (formerly COVID-19 Vaccine Moderna) to allow for third dose heterologous boosting (that is, for someone having a different vaccine to their primary course as a booster). We have also shortened the interval between the primary course and booster dose from at least 6 months to at least 3 months.

Please see the Decision page on our website, which has more details about the Spikevax vaccine for COVID-19.

Summaries of Yellow Card reporting and other recent MHRA publications

We continue to publish a summary 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 includes other data such as usage of COVID-19 vaccines and relevant epidemiological data. The report is updated regularly to include other safety investigations carried out by the MHRA under the COVID-19 Vaccine Surveillance Strategy.

We have also recently:

- updated the shelf life for Comirnaty 10 micrograms/dose mRNA Vaccine (orange cap) from 9 months to 12 months. Please see the Decision page which has more details about the Pfizer/BioNTech vaccine for COVID-19 (Comirnaty)
- updated the product information for Spikevax to include a warning on the risk of flare-ups of capillary leak syndrome (CLS) in individuals who already have CLS. The batch site address and Marketing Authorisation Holder address has also been updated.

We previously included summaries of latest COVID-19 information, including in the March 2022, April 2022 and May 2022 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 adverse reactions 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.

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Letters and medicine recalls sent to healthcare professionals in May 2022

Letters

In May 2022, the following letters were sent or provided to relevant healthcare professionals:

- Rucaparib (Rubraca): interim data from Study CO-338- 043 (ARIEL4) in the treatment indication show a decrease in overall survival compared to standard of care
- Accupro (quinapril hydrochloride): recall of tablets due to presence of nitrosamines above the acceptable daily intake level – advice for prescribers on impact on patient treatment. See accompanying medicine recall below for more information
- Zovirax (aciclovir) I.V. 500mg: batches identified containing Package Leaflets with incorrect dosing instructions. See accompanying medicine notification on page 12 for more information
- Zejula ▼ (niraparib) 100mg capsules: Interim Supply of UK (Northern Ireland) Stock to Mitigate Supply Disruption
- Vaxzevria, suspension for injection COVID-19 Vaccine (ChAdOx1-S [recombinant]): supply of Great Britain-labelled stock in Northern Ireland
- Abraxane (paclitaxel albumin), 5mg/ml powder for suspension for injection: supply of Republic of Ireland stock to UK (Northern Ireland) from May 2022 to October 2022
- Important shelf-life update for COMIRNATY ▼10 micrograms/dose concentrate for dispersion for injection (tozinameran), COVID-19 mRNA Vaccine (nucleoside-modified) for children 5 to 11 years - Great Britain and Northern Ireland
- Natpar (parathyroid hormone (rDNA)) 100 micrograms/dose powder and solvent for solution for injection: expected shortage from 30th June 2022
- Lymphoseek (tilmanocept) 50 micrograms kit for radiopharmaceutical preparation: temporary 12 month extension of shelf life of LOT 347446

Medicine Recalls and Notifications

In May 2022, recalls and notifications for medicines were issued on:

Class 2 Medicines Recall: Pfizer Limited, Accupro 5mg, 10mg, 20mg, 40mg film-coated tablets, EL(22)A/21. Issued 5 May 2022. As noted in the May 2022 Drug Safety Update, Pfizer Ltd are voluntarily recalling all stock of Accupro (quinapril hydrochloride) film-coated tablets as a precautionary measure due to the identification of a nitrosamine above the acceptable limit. Based on the available data, there is no immediate risk to patients who have been taking this medication. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier. Healthcare professionals should advise patients not to discontinue Accupro without consulting their prescriber as there are potential risks associated with suddenly stopping treatment for blood pressure. A letter was sent to prescribers in May 2022.

Class 2 Medicines Recall: Quadrant Pharmaceuticals Ltd, Mefenamic Acid 500mg film coated tablets, EL (22)A/23. Issued 17 May 2022. A batch of mefenamic acid 500mg film coated tablets is being recalled due to some tablets possessing a defective film coating resulting in the tablet core being partially exposed. This is a precautionary recall and the Marketing Authorisation Holder had not received any reports of adverse reactions related to the issue Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Class 4 Medicines Defect Information: GlaxoSmithKline UK Ltd, Zovirax I.V. 500 mg, EL (22)A/22. Issued 9 May 2022. Batches of Zovirax intravenous (I.V.) 500mg have been identified to contain an incorrect version of the Summary of Product Characteristics and Patient Information Leaflet. These incorrect versions contain unapproved text on dosage for obese adults and on dosage adjustments in renal impairment for infants and children. Healthcare professionals prescribing and administering this product should refer to the corrected and approved Package Leaflet and discard the incorrect version inside the sealed packs. A letter was sent to prescribers in May 2022.

Class 2 Medicines Recall: hameln pharma ltd, Water for Injections BP – 100ml vial, EL (22)A/24. Issued 25 May 2022. Batches of water for injections BP 100ml vial are being recalled. This is a precaution as vials may no longer be in line with licensed product specification regarding pH and conductivity. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Class 4 Medicines Defect Information: Orifarm UK Ltd, Loprazolam 1mg Tablets, EL (22)A/25. Issued 26 May 2022. Batches of Loprazolam (loprazolam mesylate) 1mg tablets have been identified to contain Patient Information Leaflets where the title incorrectly states the product name as ‘lorazolam’. Healthcare professionals are advised to inform patients of this discrepancy when dispensing packs from this batch.

Company led medicines recall: Consilient Health UK Ltd, Invita D3 800 IU Soft Capsules, CLMR (22)A/03. Issued 30 May 2022. A batch of Invita D3 800 IU (cholecalciferol) soft capsules is being recalled by the company as limited number of units were distributed prior to batch release. There are no indications of any quality of safety concerns and this recall is precautionary due to the regulatory non-compliance. Stop supplying the batch immediately, quarantine all remaining stock and return to the company.

Class 4 Medicines Defect Information: Esomeprazole 40mg Powder for Solution for Injection/Infusion, EL (22)A/26. Issued 31 May 2022. A batch of Esomeprazole 40mg Powder for Solution for Injection or Infusion has been identified with an incorrect Global Trade Item Number (GTIN). The incorrect GTIN on the batch is 05026468771424 which scans as acetylcysteine 200mg/ml injection (2g/10ml ampoules). Healthcare professionals should not use the GTIN barcode for any dispensing activities for the affected batch.

Medical Device Safety Information

A recent MHRA National Patient Safety Alert has been published on:

National Patient Safety Alert: NovoRapid PumpCart in the Roche Accu-Chek Insight insulin pump: risk of insulin leakage causing hyperglycaemia and diabetic ketoacidosis (NatPSA/2022/004/MHRA). Issued 26 May 2022. See the article in this issue of Drug Safety Update.

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

Sign-up to receive MHRA alerts about drugs and medical devices and subscribe to Drug Safety Update.

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