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 remind healthcare professionals prescribing the antipsychotic aripiprazole of the risk of addictive gambling and other impulse control disorders. Healthcare professionals should advise patients, their families and friends to be alert to these risks. Awareness of this risk must increase among patients and prescribers, as gambling is recognised as a common risk factor linked to suicide and is included within the suicide prevention in England: 5-year cross sector strategy

Next we advise that there have been case reports in the literature describing cobalt sensitivity-type reactions in patients being treated for vitamin B12 deficiency with hydroxocobalamin or cyanocobalamin, which both contain cobalt. Healthcare professionals prescribing vitamin B12 products to patients with known cobalt allergy should advise patients to be vigilant for signs and symptoms of cobalt sensitivity and treat as appropriate.

On page 8 see letters and medicine recalls sent to healthcare professionals in November 2023 including an important alert to healthcare organisations asking them to prepare for new regulatory measures for oversight of prescribing of valproate to new patients and existing female patients.

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Aripiprazole (Abilify and generic brands): risk of pathological gambling

Healthcare professionals prescribing aripiprazole are reminded to be alert to the risk of addictive gambling and other impulse control disorders. Healthcare professionals should advise patients, their families and friends to be alert to these risks.

Advice for healthcare professionals:

- there has been an increase in the number of Yellow Card reports of gambling disorder and pathological gambling associated with aripiprazole use; concerns have also been raised about a lack of awareness of this issue
- the UK reports occurred in patients with and without a prior history of gambling disorder and the majority were reported to resolve upon reduction of dose or stopping treatment with aripiprazole
- advise patients and their caregivers to be alert to the development of new or increased urges to gamble and other impulse control symptoms, such as excessive eating or spending, or an abnormally high sex drive
- consider dose reduction or stopping the medication if a patient develops these symptoms
- awareness of this risk must increase among patients and prescribers, as gambling is recognised as a common risk factor linked to suicide and is included within the suicide prevention in England: 5-year cross sector strategy
- report suspected adverse drug reactions associated with aripiprazole on a Yellow Card

Advice for healthcare professionals to provide to patients, parents and carers:

- aripiprazole is a medicine that helps with the management of schizophrenia and bipolar disorder
- do not stop taking aripiprazole without first discussing this with your doctor
- before taking aripiprazole, inform your doctor if you have any personal history of excessive gambling behaviour or impulse control disorders
- tell your doctor if you or your family or friends notice that you are developing urges or cravings to behave in ways that are unusual for you, including behaviours such as addictive gambling, excessive eating or spending, or an abnormally high sex drive

Review of pathological gambling associated with aripiprazole

Aripiprazole belongs to a class of medicines called antipsychotics. Aripiprazole has 3 approved indications: treatment of schizophrenia in adults and adolescents aged over 15 years; short-term treatment of moderate to severe manic episodes in Bipolar I Disorder in adults and adolescents aged 13 years and older; and prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

The MHRA has received reports from stakeholders raising concerns about a lack of awareness of the association between aripiprazole and the development or worsening of addictive gambling behaviours. Since the beginning of 2023, there has been an increased number of Yellow Card reports for aripiprazole which include gambling, gambling disorder or obsessive-compulsive disorder.

A review of the available evidence was considered by the Neurology, Pain and Psychiatry expert advisory group (NPPEAG) of the Commission on Human Medicines (CHM). The NPPEAG noted that the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL) for aripiprazole contain information regarding pathological gambling and other impulse control disorders. The SmPC states that impulse control disorders may result in harm to the patient and others if not recognised and advises consideration of dose reduction or stopping the medication if a patient develops increased urges while taking aripiprazole. In reviewing this issue, the NPPEAG recommended that the MHRA remind healthcare professionals and patients of these risks.

UK reports of pathological gambling and gambling disorder with aripiprazole

From 30 June 2009 to 28 August 2023, the MHRA received 69 Yellow Card reports citing aripiprazole as a suspect medicine for side effects of gambling or gambling disorder. Thirty-two of these reports were received in 2023. Fourteen reports were also received describing obsessive-compulsive disorders, or related symptoms, with aripiprazole. Aripiprazole is a frequently prescribed antipsychotic medication and usage has been steadily increasing over the past four years.[1] It is not possible to determine the frequency of these side effects from the currently available data.

Across the 69 reports of gambling and gambling disorder, most reports concerned people aged 20 to 40 years, although there were reports in patients up to 60 years of age. In many cases the patients had no previous history of gambling behaviour. Eight of the cases described patients who had lost significant sums of money and accrued considerable debts. In the majority of cases, cessation of aripiprazole led to a marked reduction or total loss of impulses to gamble. Several of the cases mention that the patient was not aware of this side effect. Awareness of this risk must increase among patients and prescribers, as gambling is recognised as a common risk factor linked to suicide and is included within the suicide prevention in England: 5-year cross sector strategy.

Report suspected reactions on a Yellow Card

Please continue to report suspected adverse drug reactions to the Yellow Card scheme. Your report will help us safeguard public health. 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.

References

1. OpenPrescribing: 4.2.1: Antipsychotic drugs – High-level prescribing trends for Aripiprazole. https://openprescribing.net/chemical/0402010AD/

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Vitamin B12 (hydroxocobalamin, cyanocobalamin): advise patients with known cobalt allergy to be vigilant for sensitivity reactions

The medicines used to treat vitamin B12 deficiency (hydroxocobalamin, cyanocobalamin) contain cobalt. There are case reports in the literature describing cobalt sensitivity-type reactions in patients being treated for vitamin B12 deficiency. Healthcare professionals prescribing vitamin B12 products to patients with known cobalt allergy should advise patients to be vigilant for signs and symptoms of cobalt sensitivity and treat as appropriate.

Advice for healthcare professionals:

- cobalt sensitivity reactions typically present with cutaneous symptoms of chronic or subacute allergic contact dermatitis. Infrequently, cobalt allergy may trigger an erythema multiforme-like reaction. Symptom onset may be immediate or delayed up to 72 hours post-administration
- cobalt allergy is estimated to affect 1 to 3% of the general population [1]
- if cobalt sensitivity-type reactions occur, assess the individual benefits and risks of continuing treatment and, if necessary to continue, advise patients on appropriate management of symptoms
- report suspected adverse drug reactions (ADRs) to the Yellow Card scheme

Advice for healthcare professionals to provide to patients and caregivers:

- hydroxocobalamin and cyanocobalamin are forms of vitamin B12 which are used to treat vitamin B12 deficiency; hydroxocobalamin is available in injectable form only, while cyanocobalamin is available in oral and injectable forms
- as vitamin B12 contains cobalt, patients with known cobalt allergy are advised to speak to a doctor or healthcare professional if they are prescribed vitamin B12
- patients with known cobalt allergy should be alert for symptoms of cobalt sensitivity-type reactions following administration of vitamin B12 products for vitamin B12 deficiency
- talk to a doctor or healthcare professional if you are given or are taking vitamin B12 and you develop allergic skin reactions such as a rash or hives
- seek urgent medical care if you experience symptoms of a serious allergic reaction (with symptoms such as extensive or blistering rash, wheeze, difficulty breathing, feeling faint)

Review of vitamin B12 and cobalt allergy

Hydroxocobalamin and cyanocobalamin are oral and injectable forms of vitamin B12 that are used to treat vitamin B12 deficiency. Endogenous vitamin B12 and these medicines contain a cobalt component.

The MHRA received a query from a member of the public, as part of a report to the Yellow Card scheme of a suspected reaction associated with vitamin B12 treatment and cobalt allergy. As a result of this, we conducted a review of this topic.

There is evidence within the literature of cobalt sensitivity reactions occurring following administration of vitamin B12. Additionally, the MHRA received three Yellow Card reports including the case described above, which report vitamin B12 as a suspect drug and possible allergic reactions to cobalt. Following the MHRA's review, it was considered appropriate to improve awareness that hydroxocobalamin and cyanocobalamin medicines contain cobalt.

We have subsequently requested relevant Marketing Authorisation Holders (MAHs) to update the Summary of Product Characteristics (SmPC) to include that vitamin B12 contains cobalt. We have also requested MAHs to update the Patient Information Leaflet (PIL) to advise patients that cobalt is contained within vitamin B12 and that they should talk to a healthcare professional if they have a known cobalt allergy.

Characteristics of cobalt sensitivity reactions and their management

Patients with a cobalt sensitivity may present with cutaneous symptoms such as chronic or subacute allergic contact dermatitis. Cobalt allergy may also trigger an erythema multiforme-like eruption. [2] The hypersensitivity reaction may be immediate or delayed to 12 to 72 hours following exposure. [3,4] Additional vigilance may be required beyond this time period.

There is no alternative treatment for vitamin B12 deficiency, therefore, vitamin B12 use is not contraindicated in patients with cobalt allergy that presents only as cutaneous symptoms. However, where previous serious allergic reaction is established in known cobalt allergy patients, individual assessment of the benefits and risks should be conducted before starting treatment.

Hydroxocobalamin products which are indicated in the treatment of known or suspected cyanide poisoning are excluded from these precautions, considering it is a medical emergency in which the potentially life-saving benefit of treatment would outweigh the risk of allergic reaction.

Patients and carers should be reminded about the symptoms of cobalt sensitivity and to seek medical advice if they experience these symptoms. Symptoms should be monitored and treated as clinically appropriate.

Report any suspected adverse drug reactions

Please continue to report 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.

References

1. Thyseen JP and Menné T. 'Metal allergy--a review on exposures, penetration, genetics, prevalence, and clinical implications'. Chem Res Toxicol 2010: volume 23, issue 2, pages 309–318
2. Ramirez-Hernandez M and others. 'Cobalt Contact Dermatitis'. Encyclopedia of Medical Immunology. Springer 2014: pages 129–132.
3. Jacob SE and others. 'Systemic Contact Dermatitis'. Dermatitis 2008: volume 19, pages 9–15.
4. Marwa K and others. 'Type IV Hypersensitivity Reaction'. StatPearls 2023.

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Letters and medicine recalls sent to healthcare professionals in November 2023

A summary of recent letters and notifications sent to healthcare professionals about medicines and medical devices, and a recent National Patient Safety Alert asking organisations to put a plan in place to implement new regulatory measures for valproate.

Valproate National Patient Safety Alert

On 28 November 2023, we issued a National Patient Safety Alert that asked organisations to put a plan in place to implement new regulatory measures for sodium valproate, valproic acid and valproate semisodium (valproate).

This follows a comprehensive review of safety data, advice from the Commission on Human Medicines and an expert group, and liaison with clinicians and organisations. Due to the known significant risk of serious harm to a baby after exposure to valproate in pregnancy, these measures aim to ensure valproate is only used if other treatments are ineffective or not tolerated, and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme.

From January 2024, valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or unless there are compelling reasons that the reproductive risks do not apply.

Clinicians should discuss the current warnings and upcoming measures relating to valproate with their patients and consider together how it affects the patient's individual circumstances. See the Public Assessment Report for the full review of safety data and expert advice on management of the risks.

Letters

In November 2023, the following letters were sent or provided to relevant healthcare professionals:

- Diazepam Desitin 5 mg Rectal solution: Interim Supply of Dutch Labelled Tubes to Mitigate Supply Disruption
- Extended Use Beyond Labelled Expiry Date for Selected Lots of Jext® 150 mcg and 300 mcg Adrenaline Auto-Injectors
- Class 3 medicines recall: Specific batches of Fluenz Tetra Nasal Spray Suspension, Influenza vaccine (live attenuated, nasal), PLGB 17901/0324

Medicine Recalls and Notifications

In November 2023, recalls and notifications for medicines were issued on:

Class 3 Medicines Recall: AstraZeneca UK Ltd., Fluenz Tetra nasal spray suspension, EL(23)A/39: Issued 30 November 2023. AstraZeneca UK Ltd. has informed the MHRA that, following routine stability analysis, the printed expiry dates for named batches of Fluenz Tetra nasal spray suspension are incorrect.

As a precautionary measure, the expiry dates need to be reduced by up to 5 days. Healthcare professionals are advised to continue using the vaccine as directed. The vaccines may be administered safely up until the amended expiry date. After the amended expiry date, any unused products should be quarantined for return.

Medical Device Safety Information
We recently published Device Safety Information pages on the following topics:

Specific brands of carbomer eye gel: recall of AACARB eye gel, AACOMER eye gel and PUROPTICS eye gel: potential risk of infection, DSI/2023/11: Issued 24 November 2023. An investigation by UKHSA has identified a potential association of a Burkholderia cenocepacia bacterial contamination with the named eye gels. As a precautionary measure these eye gels are being recalled. UKHSA considers the risk to the public from Burkholderia cenocepacia to be very low, but some patient groups are at higher risk of adverse effects. Therefore, as a precautionary measure, the UKHSA has recommended all carbomer containing eye gels are avoided in individuals with cystic fibrosis, patients cared for in critical settings (e.g. intensive care), severely immunocompromised individuals, and those awaiting lung transplantation.

Healthcare professionals are advised to follow the actions in the field safety notice including stopping supply or prescription of the named eye gels to all patients/customers (supplied from August to November). For additional information please refer to the Device Safety Information page.

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