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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NICE has accredited the process used by the MHRA to produce Drug Safety Update guidance. More information on accreditation can be viewed on the NICE website.

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This month we inform of a possible association between valproate use by men and an increased risk of neurodevelopmental disorders in their children. We recommend precautionary advice that men and their partners should use effective contraception during valproate treatment and for at least 3 months after stopping.

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

This month the MHRA has also launched a new three-year Strategy for Improving Safety Communications, which aims to transform the way we provide information about the safety of medicines, medical devices and healthcare products in the UK to support effective implementation of new safety measures.

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Valproate use in men: as a precaution, men and their partners should use effective contraception

A retrospective observational study has indicated a possible association between valproate use by men around the time of conception and an increased risk of neurodevelopmental disorders in their children. Inform male patients who may father children of this possible increased risk and the recommendation to use effective contraception during valproate treatment and for at least 3 months after stopping valproate.

See a previous Drug Safety Update for the introduction of the prescribing requirements in patients under 55 years of age (female and male) – the new advice provided here is in addition to these measures.

No one should stop taking valproate without talking to their healthcare professional.

Information for healthcare professionals:

- findings from a retrospective observational study, combining analyses of electronic medical records in Norway, Denmark and Sweden, indicate a possible increased risk of neurodevelopmental disorders in children born to men treated with valproate in the 3 months prior to conception, compared to those born to men treated with lamotrigine or levetiracetam
- in the study, the cumulative risk of neurodevelopmental disorders ranged from 4.0% to 5.6% in the valproate treated group versus 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy treated group (pooled adjusted hazard ratio 1.50, 95% CI 1.09 to 2.07)
- this potential risk is much lower than the up to 30-40% risk of neurodevelopmental disorders in children born to mothers taking valproate during pregnancy, estimated from several studies
- the study did not include an untreated group and background risk in this patient population is therefore unknown
- an increased risk of neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. As such this advice is precautionary

Advice for healthcare professionals:

- inform male patients (of any age) who may father children of the possible risk at initiation of valproate or at their next regular treatment review – this counselling should be given irrespective of the indication for valproate and also after intravenous use of valproate
- as a precaution, recommend that male patients use effective contraception (condoms, plus contraception used by the female sexual partner) throughout the valproate treatment period and for 3 months after stopping valproate, to allow for one completed sperm cycle not exposed to valproate
- at the next regular treatment review, discuss with men on oral valproate treatment whether they are planning a family in the next year and if they are, refer to a specialist to discuss alternative treatment options
- if a female patient reports they are pregnant or planning a pregnancy with a man on valproate (including those undergoing IVF), refer for prenatal counselling

- advise men not to donate sperm during valproate treatment and for 3 months after stopping valproate
- report any suspected adverse drug reactions associated with valproate on a Yellow Card

Information for healthcare professionals to provide to patients:

- if you father a child while you are taking valproate or in the 3 months after stopping valproate, there is a potential small increased risk of the child being diagnosed with a mental or movement related developmental disorder (neurodevelopmental disorder)
- advice will be added to the valproate patient guide; in the meantime see MHRA's Advice for male patients on valproate to use contraception and visual risk communication diagram to be used by a healthcare professional when counselling on the risks

Advice for healthcare professionals to provide to patients:

- it is recommended that you and your female sexual partner should both use effective birth control (condoms and another form of female contraception) as a precaution while you are taking valproate and for at least 3 months after stopping valproate
- allow at least 3 months to pass after stopping valproate before trying to father a child
- you should not donate sperm whilst taking valproate and for 3 months after stopping
- do not stop taking valproate unless you are advised to do so by a healthcare professional
- report any suspected adverse drug reactions associated with valproate on a Yellow Card

Review of data regarding potential risk to children with paternal use of valproate

Valproate (as sodium valproate, valproic acid or valproate semisodium) is authorised for the treatment of epilepsy and bipolar disorder. It is also used outside of the licence ('off label') to treat other conditions.

During the 2018 European review into the risks of valproate in pregnancy, a number of concerns were considered about risks in all patient groups, including the potential risks to children born to fathers who take valproate. A retrospective observational study was requested by the European regulatory authority to examine any association between exposure to valproate in men and the risk of congenital abnormalities and developmental disorders, including autism, in their offspring.

The MHRA review of the findings of the study was considered by the Commission on Human Medicines (CHM). We have published a Public Assessment Report of the review.

Changes will be made to the product information available online. The Patient Information Leaflet in the box and hard-copies of the updated safety and educational materials will be available in the coming months. The current patient card will be amended to include advice for male patients in addition to the measures relating to the Pregnancy Prevention Programme for women. The manufacturers of valproate will also send a letter to relevant healthcare professionals in October 2024.

This advice is in addition to the existing requirements for oral formulations of valproate for two specialists to independently consider and document that there is no other effective or tolerated treatment or the risks are not applicable at initiation of treatment in male patients under 55 years. It is however noted that reproductive potential in male patients continues beyond 55 years and men older than 55 years on valproate should be counselled on the risk as appropriate.

Given the typical-use failure rate of condoms, it is advised that women whose sexual partners are using valproate should use effective contraception during use of valproate and for 3 months after the male partner stops valproate. It should be noted that if there is no pregnancy risk or if the woman is already using highly effective contraception, then condom use is not required to prevent pregnancy.

The potential risk to the offspring of men taking valproate around conception apply to both those taking valproate orally and intravenously (IV), however discussions with men on treatment options apply only to those taking valproate orally. For those who receive IV valproate in an acute care setting, advise the use of contraception for 3 months after treatment.

Information about the study findings

The study looked at medical records from national registries in Norway, Denmark and Sweden. There was no observed association between paternal valproate exposure and neurodevelopmental adverse outcomes in the individual country specific study results, but when the results from the three countries were pooled using meta-analysis a statistically significant association was observed.

Overall, an increased risk of neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of neurodevelopmental disorders to children born to men stopping valproate for more than 3 months prior to conception (allowing new spermatogenesis without valproate exposure).

The study was not large enough to determine the absolute risk of each of the specific neurodevelopmental disorder subtypes included in the study (autism spectrum disorder, intellectual disability, communication disorder, attention deficit hyperactivity disorder, movement disorders). Study limitations included potential confounding by indication.

The study used secondary data, therefore data on some known risk factors and causal factors for neurodevelopmental disorders were not available. There was also a difference in follow-up time between comparator groups which may impact the findings. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2

years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Further studies and data are needed to better understand this risk.

Proposed mechanism of action paternal transmission

The 2018 European review considered the potential mechanisms for paternal transmission of adverse effects of valproate. These included the valproate level of the seminal fluid of patients treated with valproate, evidence for genetic changes in the sperm DNA and evidence for epigenetic changes. It is noted that concentrations of valproate in the semen are 25,000 times less than concentrations that would be present in maternal plasma after a standard dose of valproate and so this mechanism of transfer is considered unlikely. Further studies are being performed to evaluate the possible impact of valproate on the genome and epigenome of germ cells.

There have been reports of infertility in men taking valproate but the mechanism of this is unclear. Preclinical data shows testicular toxicity in both juvenile and adult animals. Some preclinical data has also shown behavioural abnormalities transferred via the maternal and paternal lines through to the third generation. A CHM epigenetics Expert Working Group is currently considering evolving data on the potential for valproate to be associated with epigenetic effects, including the histone deacetylase (HDAC) inhibitory properties of valproate.

Report suspected reactions on a Yellow Card

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.

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This article was issued on 5 September, ahead of the rest of the September 2024 issue.

Letters and medicine recalls sent to healthcare professionals in August 2024

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

Letters

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

- Dexdor 100 micrograms/ml concentrate for solution for infusion (Dexmedetomidine): Interim Supply of ROI/NI (EU license) Stock to Mitigate Supply Disruption

- Rabipur (Rabies vaccine, inactivated), powder and solvent for solution for injection in pre-filled syringe: Reports of rubber particles after reconstitution - recommendations to minimise the risk of particles

- Eudemine Tablets (Diazoxide): Notification on storage conditions for Eudemine 50mg Tablets PL 36301/0021

- Mydrane 0.2 mg/ml + 3.1 mg/ml + 10 mg/ml solution for injection (Tropicamide, Phenylephrine hydrochloride, Lidocaine hydrochloride monohydrate): Interim Supply of Polish Stock to Mitigate Supply Disruption

Medicine Recalls and Notifications

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

Class 4 Medicines Defect Information: Sandoz Limited, Omeprazole products, EL(24)A/34. Issued 7 August 2024. Sandoz Ltd. has informed the MHRA that there is missing safety information in the Patient Information Leaflet (PIL) and Summary of Product Characteristics (SmPCs) of the specific products listed in this notification.

Class 3 Medicines Recall: Accord-UK Ltd, Trandolapril 0.5mg, 2mg, 4mg Capsules, EL(24)A/35. Issued 8 August 2024. Accord-UK Ltd is recalling the listed batches after retesting showed out of specification results. The listed batches are being recalled as a precautionary measure after testing showed variability of the Trandolapril content beyond permitted levels.

Class 4 Medicines Notification, Star Pharmaceuticals Limited, Diflucan Oral Suspension 40mg/ml, EL(24)A36. Issued 12 August 2024. Star Pharmaceuticals Limited has informed the MHRA that an error has been identified in the Patient Information Leaflet (PIL) for two batches of Diflucan Oral Suspension 40mg/ml.

Class 4 Medicines Defect Information: Dawa Limited, Trazodone Hydrochloride 50mg, 100mg Capsules & 50mg/5ml Oral Solution, EL (24)A/37. Issued 14 August 2024. Dawa Limited has informed the MHRA of an error with the Patient Information Leaflets

(PILs) that have been packed in the listed batches of Trazodone Hydrochloride 50mg and 100mg Capsules and Trazodone Hydrochloride 50mg/5ml Oral Solution.

Class 2 Medicines Recall: Strides Pharma UK Limited, Loperamide Hydrochloride Capsules 2mg, EL(24)A/38. Issued 15 August 2024. Strides Pharma UK Ltd is recalling the listed batch as a precautionary measure due to an out of specification result for microbial contamination, reported during retesting.

Class 3 Medicines Recall: Glenmark Pharmaceuticals Europe Ltd, Fingolimod 0.5 mg Hard Capsules, EL(24)A/39. Issued 19 August 2024. Glenmark Pharmaceuticals Europe Ltd is recalling this batch after retesting showed out of specification results. The tabled batches are being recalled as a precautionary measure after testing showed variability of the capsule contents beyond permitted levels.

Class 4 Medicines Defect Information: Chemidex Pharma Ltd, Ponstan 250mg Capsules & 500mg Tablets (mefenamic acid), EL(24)A/40. Issued 27 August 2024. Chemidex pharma ltd has informed the MHRA that the patient information leaflet (PIL) in the cartons for the batches listed in the tables for Ponstan 250mg capsules and Ponstan Forte 500mg tablets include an out of date PIL, dated March 2020 and January 2021 respectively.

Medical Device Safety Information

We recently published Device Safety Information pages on the following:

CPT Hip System Femoral Stem 12/14 Neck Taper: Increased Risk of Postoperative Periprosthetic Femoral Fracture, DSI/2024/007. Issued 4 September 2024. Recent research has found that the CPT Hip System Femoral Stem 12/14 Neck Taper, cobalt chromium, (a type of hip implant) carries a higher risk of postoperative periprosthetic femoral fracture (PFF) compared to hips of a similar design but made of a different material. The device will be phased out in the UK by December 2024. For additional information please refer to the Device Safety Information page and the Field Safety Notice.

Philips Respironics BiPAP A series ventilators: alarm malfunction and risk of therapy interruptions in ventilators not intended for life-support, DSI/2024/006. Issued 28 August 2024. Philips Respironics has issued a Field Safety Notice (FSN) relating to the Bilevel Positive Airway Pressure (BiPAP) A series ventilators. This relates to a Ventilator Inoperative alarm which could result in the potential loss of therapy to patients without warning. For additional information please refer to the Device Safety Information page and the Field Safety Notice.

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