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

	Isotretinoin (Roaccutane▼): introduction of new safety measures, including additional oversight of the initiation of treatment for patients under 18 years of age	page 2
·	**MedSafetyWeek November 2023: your Yellow Card report helps to improve patient safety**	page 6
	Valproate: dispense full packs of valproate-containing medicines	page 8
	Letters and medicine recalls sent to healthcare professionals in August 2023	page 9

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.

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.

To subscribe to monthly email alerts of Drug Safety Update see: https://www.gov.uk/drug-safety-update

In our first article, we advise of the introduction of additional oversight of the initiation of isotretinoin in patients under 18 years and strengthened assessment and monitoring of mental health and sexual function issues. We ask healthcare professionals to review these new measures and supporting materials and integrate them into their clinical practice when referring patients and when prescribing or dispensing isotretinoin.

Second we provide information on the eighth annual #MedSafetyWeek social media campaign, which will take place from 6 to 12 November 2023. We ask healthcare professionals to support the campaign and talk to their patients and colleagues about side effects and how to report suspected problems to the Yellow Card scheme.

Third, we remind of the new guidance for dispensing of valproate-containing medicines in the manufacturer's original full pack, following amendments to the Human Medicines Regulations (HMRs). See page 8 for more information and a link to our guidance.

Our final article provides a summary of recent letters and notifications sent to healthcare professionals about medicines. If you have been forwarded this issue of Drug Safety Update, subscribe directly via our website.

Isotretinoin (Roaccutane▼): introduction of new safety measures, including additional oversight of the initiation of treatment for patients under 18 years of age

We have strengthened the safe use of isotretinoin through the introduction of additional oversight of the initiation of isotretinoin in patients under 18 years and through improved assessment and monitoring of mental health and sexual function issues. We ask healthcare professionals to review these new measures and supporting materials and integrate them into their clinical practice when referring patients and when prescribing or dispensing isotretinoin.

Summary of measures

- 2 independent prescribers need to agree the initiation of isotretinoin in patients under 18 years
- new counselling requirements about potential mental health and sexual function side effects
- assessment of mental health and sexual function before starting treatment and monitoring of mental health and sexual function during treatment
- new roles and responsibilities for healthcare professionals
- new regulatory risk minimisation materials

Following the April 2023 recommendations, the Isotretinoin Implementation Advisory Expert Working Group of the Commission on Human Medicines (CHM) has developed guidance to support the safe implementation of the new regulatory position – consult the Report of the Isotretinoin Implementation Advisory Expert Working Group.

Advice for healthcare professionals:

- all patients must be counselled about the benefits and risks of treatment before isotretinoin is prescribed, including possible mental health and sexual function side effects; we also ask the referrer (usually the GP) to provide information about isotretinoin to the patient and provide counselling (where possible) regarding the benefits and risks of isotretinoin treatment
- isotretinoin is teratogenic; all patients of child-bearing potential must be entered into the Pregnancy Prevention Programme
- prescribers should assess patients' mental health before prescribing isotretinoin including the use of patient-reported outcome measures
- ask patients about any sexual function concerns before prescribing isotretinoin
- give the patient sufficient time to consider, reflect and ask questions before starting isotretinoin treatment
- use the new regulatory risk minimisation materials with all patients: Acknowledgement of Risk Form, Patient Reminder Card, Pharmacist Checklist
- the Lead Prescriber, who initiates isotretinoin treatment, must have expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements
- initiation of isotretinoin treatment in patients under 18 years of age now requires agreement by 2 independent healthcare professionals that there is no other appropriate effective treatment before it is prescribed.

This means that isotretinoin should only be prescribed for severe acne that is resistant to adequate courses of standard therapy

- review patients approximately 1 month after initiation of treatment in a face-to-face (in-person) appointment
- monitor patients for side effects including mental health and sexual function side effects at each follow up appointment including objective mental health patient reported outcome measures
- any healthcare professional involved in the treatment of patients with acne, particularly prescribers of isotretinoin, should review the full details of the new requirements in the Report of The Commission on Human Medicines Isotretinoin Implementation Advisory Expert Working Group
- report suspected adverse drug reactions associated with isotretinoin on a Yellow Card

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

- isotretinoin is an effective treatment for acne. It should be used for acne that is severe or at risk of causing permanent scarring when other appropriate treatments have not been effective
- all medicines have side effects. Not every patient experiences side effects, but you should know about them and what to do if they occur. This includes possible mental health and sexual function side effects
- inform your healthcare professional if you have any personal or family history of mental health issues or any sexual function concerns
- isotretinoin if taken during pregnancy can seriously harm an unborn baby. Patients **must not** become pregnant during treatment with isotretinoin and for 1 month after isotretinoin is stopped
- if you may be able to get pregnant your doctor must enter you into the Pregnancy Prevention Programme before you are treated with isotretinoin
- take time to think about the information provided by your doctor about the benefits and risks of isotretinoin and decide whether it is the right treatment for you
- your doctor will check that you understand the information in the Acknowledgement of Risk Form – you need to agree to all applicable points in the Acknowledgement of Risk Form in order to receive isotretinoin; make sure to keep your copy of the completed form safe
- read the Patient Reminder Card and keep it safe. It contains important safety information that you need to be aware of before and during treatment.
- if you are under 18 years of age, 2 healthcare professionals must agree that there is no other appropriate effective treatment option before you start isotretinoin
- patients already being treated with isotretinoin should continue to follow their agreed treatment plan from their prescriber, but seek medical advice if they have any side effects or concerns
- report side effects associated with isotretinoin directly to the MHRA via the Yellow Card scheme

Isotretinoin treatment and new safety measures

Isotretinoin should only be prescribed for severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy. Isotretinoin capsules are also known by the brand names Roaccutane and Reticutan in the UK.

In April 2023, the Commission on Human Medicines (CHM) published recommendations following their review of mental health and sexual side effects suspected to be associated with isotretinoin. The review considered all the available evidence, including information from patients and their families, and recommended new measures to strengthen the safety of isotretinoin treatment.

The product information for isotretinoin medicines has been updated following the review's recommendations. This includes the addition of new warnings and precautions on potential mental health and sexual function side effects to the product information and the requirement for 2 healthcare professionals to agree that there is no other appropriate effective treatment in patients under 18 years of age.

Isotretinoin Implementation Advisory Expert Working Group
Following their review, the CHM formed an Isotretinoin Implementation Advisory Expert Working Group, composed of experts and representatives of the healthcare organisations to advise on how best to implement the recommendations in clinical practice. The CHM endorsed the guidance from the Isotretinoin Implementation Advisory Expert Working Group.

New guidance

The Isotretinoin Implementation Advisory Expert Working Group has worked with the MHRA to develop guidance specifying which healthcare professionals have the appropriate expertise to be the:

- Lead Prescriber, who makes the decision to initiate isotretinoin treatment
- Second Approved Named Healthcare Professional who agrees that isotretinoin is the most appropriate treatment option for adolescents under 18 years of age
- Follow-Up Prescriber responsible for continuing and monitoring isotretinoin treatment

The Lead Prescriber must have expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.

The Isotretinoin Implementation Advisory Expert Working Group also developed guidance on the assessment and monitoring of mental health and sexual function.

For further details see the Report of the CHM Isotretinoin Implementation Advisory Expert Working Group.

New regulatory risk minimisation materials

New compulsory regulatory risk minimisation materials have been developed for use with all patients consisting of an Acknowledgement of Risk Form, a Patient Reminder Card and a Pharmacist Checklist. These are available electronically and will be sent to relevant healthcare professionals, including dermatology teams and pharmacy services GP practices, by post.

The Acknowledgment of Risk Form must be completed with all patients initiating isotretinoin treatment.

The new Acknowledgment of Risk Form has been developed to:

- continue to record the patient's acknowledgment of the known risk of harm to unborn babies during pregnancy
- record acknowledgment of other risks including possible mental health and sexual function side effects
- continue to record enrolment onto the revised Pregnancy Prevention Programme if the patient is of childbearing potential
- record the agreement of 2 independent healthcare professionals that there is no other appropriate effective treatment in patients under 18 years of age

A package of additional supporting documents has also been developed by the British Association of Dermatologists, British Dermatology Nursing Group and other stakeholders to support these changes. These additional documents can be adapted to local needs and systems.

All healthcare professionals involved in the treatment of patients who may require isotretinoin should refer to the Report of the CHM Isotretinoin. Implementation Advisory Expert Working Group for further details, including a description of the isotretinoin treatment pathway.

Report any reactions on a Yellow Card

Isotretinoin is a black triangle medicine and all suspected adverse reactions, including any sexual and psychiatric adverse reactions, should be reported via the Yellow Card scheme. Reports can be made of suspected reactions experienced at any time, including historic adverse experiences with medicines.

Please include in the report as much detail as possible, particularly if a side effect continued or started after treatment was stopped. Information about medical history, any concomitant medication, onset timing, treatment dates, and product brand name should also be included.

Report to the Yellow Card scheme electronically using:

- the Yellow Card scheme 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)

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MedSafetyWeek November 2023: your Yellow Card report helps to improve patient safety

The eighth annual #MedSafetyWeek social media campaign will take place from 6 to 12 November 2023. It will focus on the importance of reporting suspected adverse reactions to medicines and suspected problems with medical devices. We ask healthcare professionals to support the campaign and talk to their patients and colleagues about side effects and how to report suspected problems to the Yellow Card scheme.

What healthcare professionals can do to support MedSafetyWeek – 6 to 12 November 2023

- follow our social media channels and show your support for this year's MedSafetyWeek by retweeting, commenting, liking, and sharing material with your social media contacts using #MHRAyellowcard, #MedSafetyWeek, #ReportSideEffects and #patientsafety
- never delay in reporting suspected adverse drug reactions (side effects) to the Yellow Card scheme or via the Yellow Card app (download from the Apple App Store or Google Play Store) – only a suspicion is needed to report a suspected reaction to us
- report suspected side effects to medicines, adverse incidents with medical devices (including software, apps and artificial intelligence), safety concerns about e-cigarettes and their refills, adverse reactions to herbal or homeopathic medicines, and defective, low-quality or falsified (fake) healthcare products
- report suspected adverse reactions associated with COVID-19 vaccines and medicines, as well as suspected incidents with medical devices and test kits, directly to the Coronavirus Yellow Card reporting site or use the Yellow Card app
- discuss with your patients:
    - the importance of taking the right medicine, at the right time, in the right way, and at the right dose and of carefully following instructions for use of medical devices
    - the importance of reading the Patient Information Leaflet that comes with a medicine or vaccine
    - what to do if they experience problems with a healthcare product, such as contacting a healthcare professional and reporting to the Yellow Card scheme
- talk to your colleagues about being vigilant for suspected adverse reactions with medicines or vaccines, especially new, serious or rare reactions or those that may have a delayed onset, and the importance of reporting them to the Yellow Card scheme

About MedSafetyWeek

MedSafetyWeek is an annual event. It forms part of international efforts to raise awareness about the importance of reporting suspected adverse reactions to national medicines regulatory authorities, such as the MHRA. This year, regulators from over 80 countries will take part.

The theme for 2023's campaign is 'Who can report?' All patients, carers, and healthcare professionals can contribute and play a key role in improving patient safety and strengthening the vigilance of healthcare products. You can read more about the global MedSafetyWeek campaign on the Uppsala Monitoring Centre's website.

This MedSafetyWeek, we remind you to report suspected adverse drug reactions to a medicine or vaccine directly to the Yellow Card scheme as soon as they arise. Do not wait or rely on someone else to report concerns. Only a suspicion is needed to submit a Yellow Card so, if in doubt, please do complete a report.

About Yellow Card reports

The Yellow Card scheme helps us to monitor the safety of healthcare products once they are on the market. Reporting to the scheme allows the MHRA to identify new adverse effects and gain more information about known adverse effects. By completing a Yellow Card report, you help contribute to the safe use of healthcare products for patients.

Please report any adverse incident associated with a medicine or medical device through the Yellow Card scheme and local reporting systems. Potential problems with medical devices can also be reported.

It is particularly important that all suspected adverse reactions involving Black Triangle medicines are reported. Yellow Card reports can also be made for products such as blood factors and immunoglobulin products, herbal or homeopathic medicines, and e-cigarettes and their refill containers (e-liquids). Read more about the different types of Yellow Card reports on the Yellow Card website.

The Yellow Card scheme has helped to identify numerous safety issues, many of which were not previously linked to a particular healthcare product until Yellow Card reports were received by the MHRA. Read our case studies describing how Yellow Card reports have contributed to patient safety.

Resources for healthcare professionals

More information and resources, such as accredited e-learning modules and materials to help raise awareness locally in general, are available on the Yellow Card website. Links to new materials to download and print for local promotion and social media will be added to the MedSafetyWeek campaign page by the end of October.

Healthcare professionals should also speak to their local Medication Safety Officer (MSO) or one of our six Yellow Card centres to help support the campaign locally and help raise awareness. You can also discuss with your local Medical Device Safety Officer (MDSO) how you can help support the reporting of adverse incidents with medical devices.

Please encourage your colleagues to sign up to receive alerts for Drug Safety Update and other safety information from the MHRA about medicines and medical devices. These messages are also available through the Yellow Card app (download from the Apple App Store or Google Play Store).

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Valproate: dispense full packs of valproate-containing medicines

Unless there are exceptional circumstances, valproate-containing medicines must always be dispensed in the manufacturer's original full pack.

Following a consultation, the Government has amended the Human Medicines Regulations 2012 (HMRs) to require manufacturer's original full pack dispensing of valproate-containing medicines.

We published guidance for dispensing of valproate-containing medicines.

The change came into force in England, Scotland and Wales on 11 October 2023. While the legislative change currently does not apply to Northern Ireland, the guidance on dispensing valproate-containing medicines should be considered by pharmacists in Northern Ireland as good practice.

Unless there are exceptional circumstances, valproate-containing medicines must always be dispensed in the manufacturer's original full pack from 11 October 2023. You must either round up or down so that the patient receives their supply in the manufacturer's original full pack and ensure that they receive an amount that is as close as possible to that prescribed. You must not subsequently re-package any valproate-containing medicine into plain dispensing packaging.

The aim of amendments to require manufacturer's original full pack dispensing of valproate-containing medicines is to ensure that women always receive information about the harms of valproate during pregnancy. This will further decrease the number of babies who are exposed to valproate in pregnancy.

The change in practice will ensure that patients (male and female) are provided with the specific warnings and pictograms on the labelling and a detachable patient card, along with the statutory Patient Information Leaflet

The manufacturer's original full pack does not have to be supplied where a risk assessment is in place that refers to the need for the patient to be sold or supplied valproate-containing medicines in different packaging (for example, in a monitored dosage system) and there are processes in place to make sure that the patient receives the Patient Information Leaflet.

Dispensers of valproate are also reminded to provide patients of childbearing potential with the patient card (if not affixed to pack) and patient guide as part of the Pregnancy Prevention Programme.

See our published guidance for more information about these measures and why the rules on dispensing valproate-containing medicines have been changed.

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Letters and medicine recalls sent to healthcare professionals in September 2023

A summary of recent letters and notifications sent to healthcare professionals about medicines and medical devices, and information about the publication of recent Device Safety Information pages.

Letters

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

- Azathioprine 75 mg & 100 mg tablets: Risk of overdose if wrong dose prescribed or dispensed
- Fotivda 890 mcg hard capsules (tivozanib): Interim Supply of Dutch Language Stock to Mitigate Supply Disruption
- Paracetamol 10mg/ml solution for infusion PL 46788/0008 - Blushing of PVC bags
- Vaxneuvance▼ (pneumococcal polysaccharide conjugate vaccine (15-valent, adsorbed)) suspension for injection in pre-filled syringe: Important information regarding the potential for breakage of Vaxneuvance pre-filled syringes

Medicine Recalls and Notifications

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

Class 3 Medicines Recall: Theramex HQ UK Ltd, Evorel Sequi, EL (23)A/34: Issued 5 August 2023, Theramex has informed the MHRA that some cartons of Evorel Sequi contain the incorrect combination of patches. Healthcare professionals are advised to stop supplying the named batches in this alert immediately, quarantine all remaining stock and return it to your supplier using your supplier's approved process. If a patient presents with the incorrect patches, they should be dispensed a correct pack from another batch. Theramex has confirmed that all other batches are unaffected and that there is no impact on supply.

Class 4 Medicines Defect Information: Colgate-Palmolive (U.K.) Limited, Duraphat 5000ppm Fluoride Toothpaste (51g), EL (23)A/35: Issued 7 August 2023, Colgate-Palmolive (U.K.) Limited has informed the MHRA that the Patient Information Leaflet (PIL), carton and tube of the batches of Duraphat 5000ppm Fluoride Toothpaste (51g) listed are missing information relating to the presence of allergens in the product. In addition, the PIL is missing information relating to the concentration of Sodium Benzoate. Healthcare professionals are advised to note the updated information. Where appropriate, inform patients about it, provide them with an updated copy of the PIL, and remind them to read the leaflet in its entirety before using the medicine.

Company led medicines recall: Sun Pharma UK Ltd, Gemcitabine 10mg/ml Solution for Infusion PL 31750/0062 (Single dose Infusion bag, 2000mg/200ml), CLMR(23)A/06: Issued 7 September 2023, Sun Pharma UK Ltd has informed the MHRA of a labelling issue with one batch of Gemcitabine 2000mg/200ml infusion. The affected infusion bags are labelled as 1800mg/180ml rather than 2000mg/200ml (though the secondary packaging is labelled correctly as 2000mg/200ml). Healthcare professionals are advised to stop supplying the affected batches immediately. Quarantine all remaining stock and liaise with the manufacturer on the return process.

Class 3 Medicines Recall: Chiesi Ltd., Trimbow 87/5/9 mcg pressurised inhalation solution, EL(23)A/36: Chiesi Ltd has informed the MHRA about a potential issue with the batches listed in this notification. Healthcare professionals are advised to stop supplying the named batches in this alert immediately, quarantine all remaining stock and return it to your supplier using your suppliers approved process.

Class 4 Medicines Defect Information: Max Remedies Ltd, Max Healthcare Paracetamol 500 mg Capsules, EL (23)A/37: Max Remedies has informed the MHRA that they have identified an infrequent printing error relating to the Braille text printed on the cartons of this product. Some characters may be incorrect leading to potential misinterpretation of the contents/strength of the product. We would advise that blind and/or partially sighted patients are instructed to follow the directions outlined in the PIL as normal and if there are concerns, they should consult with their carer, or alternatively contact Max Remedies. The quality of the capsules is not impacted by this defect and all written information on the packs is correct.

Medical Device Safety Information

We recently published a Device Safety Information page on the following topics:

No-React® cardiovascular bioprosthesis implantables: discontinuation of CE marking and manufacture. Remaining stock may continue to be used and any adverse incidents reported nationally (DSI/2023/009)

The MHRA emphasises the importance of national reporting of any suspected adverse incidents associated with the product following CE certification withdrawal and cease of manufacturing.

No-React implantable cardiovascular devices already placed on to the UK market remain legally CE marked and available for sale and use. Products already in use or on the UK market are considered safe. This includes devices held in stock by UK distributors and those already sold or supplied to UK healthcare settings. For additional information please refer to the Device Safety Information page.

SteriFeed Colostrum Collection device and risk of choking due to infant airway occlusion, DSI/2023/010

The SteriFeed colostrum collection device is intended to be used only to collect and store colostrum. The device is not designed for feeding.

However, we understand that it has also been used for feeding colostrum to babies.

We are aware of 6 incidents in which the push cap became lodged in the back of the baby's mouth when it was not removed from the top end of the syringe before being inserted into the baby's mouth for feeding. There were no fatalities, however one infant required emergency surgery.

The intended use of the device is not for directly feeding the colostrum to babies. The cap must always be removed before use. Healthcare professional advice should be sought for guidance on feeding the collected colostrum to the baby.

The manufacturer is undertaking a design change to minimise the choking hazard associated with the cap. Work is underway on this change and it will take approximately 6 months.

Healthcare professionals are advised to remove the cap before using the device. When instructing parents on using the device, remind them to always remove the cap from the tip of the syringe prior to use. Advise parents on how to feed the collected colostrum to the baby. For additional information, please refer to the Device Safety Information page and press release.

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