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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Firstly, we advise on the introduction of new labelling for topical steroids. This new information will inform on the potency of the product. This article also highlights the potential for Topical Steroid Withdrawal reactions when high potency topical steroids are used for a prolonged period of time.

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

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Topical steroids: introduction of new labelling and a reminder of the possibility of severe side effects, including Topical Steroid Withdrawal Reactions

Topical steroid products are safe and highly effective treatments for the management of a wide range of inflammatory skin diseases but have important risks, especially with prolonged use at high potency. In the coming months, as a result of regulatory action, topical steroid products will be labelled with information on their potency to simplify advice for patients.

Advice for healthcare professionals:

- adverse reactions have been reported following long-term (generally 6 months or more) use of moderate or stronger potency topical steroids, particularly when used for eczema treatment – these reactions are often referred to as 'Topical Steroid Withdrawal Reactions' (TSW)
- symptoms of TSW can include intense redness, stinging, and burning of the skin that can spread beyond the initial treatment area
- the risk of these and other serious reactions increases with prolonged use of higher potency steroid products
- over the coming year, topical steroids will be labelled with information on their potency to assist with counselling patients
- when prescribing or dispensing topical steroids, advise on the amount of product to apply, how often, where to apply it and when to stop treatment
- if previous discontinuation was associated with reactions that raise suspicion of TSW, alternative treatments should be considered
- provide support to patients living with symptoms of TSW and review treatment plans with patients
- report suspected adverse drug reactions to the Yellow Card scheme, including after discontinuation of topical steroids

Advice for healthcare professionals to give to patients and carers:

- cases of skin reactions have been reported by long-term users of topical steroids when stopping treatment, including intense redness, stinging, and burning of the skin that can spread beyond the initial treatment area (see Patient Safety Leaflet on topical corticosteroids and withdrawal reactions)
- the exact frequency cannot be determined but the reactions are estimated to be rare

- if using more than one topical steroid on different body areas, ensure you are using the correct strength for the area of the body concerned. In the future the strength will be displayed on the packaging of your medicine
- seek medical advice before using a topical steroid on a new body area as some areas may require a different topical steroid
- always apply topical steroids as instructed and read the Patient Information Leaflet provided with your medicine
- ask your prescriber or pharmacist if you have any questions about your medicines or are concerned about side effects – and report suspected side effects to the Yellow Card scheme

Background

Topical steroids are highly effective for the treatment of inflammatory skin conditions such as eczema and psoriasis, when prescribed and used appropriately. They are available in different potencies:

- mildly potent (for example, hydrocortisone)
- moderately potent (for example, clobetasone)
- potent (for example, betamethasone)
- very potent (for example, clobetasol).

The lowest potency topical steroid for effective treatment should be used and this may mean using different potency products for different body areas.

Over the coming year, topical steroids will be labelled with their potencies to aid correct selection and to simplify the advice to patients requiring multiple steroid products of differing potencies. These will be labelled ‘mild steroid’, ‘moderate steroid’, ‘strong steroid’, and ‘very strong steroid’.

Serious side effects of topical steroid products

Whilst considered safe and effective, topical steroids can rarely lead to serious side effects such as thinning of the skin, adrenal suppression or very rarely Cushing’s syndrome, due to systemic absorption. The incidence of these more serious side effects is linked to the amount, potency and duration of use of the topical steroid.

Thinned skin appears translucent with visible tiny blood vessels and may be more fragile and more susceptible to stretch marks. This can be very difficult to see in brown or black skin, therefore careful monitoring is required.

Adrenal suppression arises from overuse of topical steroids. The symptoms include low blood pressure, dizziness and fainting. This is a serious, life-threatening condition that needs urgent treatment. Stopping the topical steroid suddenly is dangerous if there is adrenal suppression, and it is likely that the individual will require oral steroid therapy replacement.

Cushing's syndrome manifests with the development of a red, puffy, rounded face, acne and excessive facial and body hair, high blood pressure, weight gain, stretch marks, slow wound healing and frequent infections.

Patients, particularly those who require prolonged use or are using very potent topical steroids, should be advised to look for these effects and seek prompt medical attention if they occur. Please review adrenal crisis guidance and information from the Society of Endocrinology and National Patient Safety alert from NHS England for further advice.

In psoriasis, use of large quantities of topical steroids is associated with a risk of more severe disease such as generalised pustular psoriasis.

Patients have also reported experiencing a less well understood group of side effects that has been termed Topical Steroid Withdrawal (TSW) reactions. TSW is the generally accepted patient-led term for these reactions - this group of conditions do not necessarily meet the medical pharmacological definition of withdrawal. Whilst these are still poorly understood groups of reactions, the evidence to date is that these reactions typically occur in four stages:[1,2]

1. A few days (usually) after discontinuation, there is an acute eruption of burning red, exudative skin which may extend to untreated areas.
2. Skin becomes dry and itchy with shedding (desquamation).
3. Skin starts to recover but is more sensitive and intermittent flares may occur.
4. Skin recovers to the state prior to topical corticosteroid cessation. The recovery process may be prolonged.

Continued use of topical steroids should be re-evaluated and alternative treatment options explored if a suspected TSW has occurred. Further information on TSW can be found in the September 2021 Drug Safety Update.

Review of Topical Steroid Withdrawal

Since our last review of this issue in 2021 we have continued to receive reports and concerns from patients regarding TSW. The MHRA has carefully reviewed information received since the last review of this risk, and sought advice from the Commission on Human Medicines, with clinical experts in dermatology and representatives from dermatology charities being included in these discussions.

During our review, data gathered from Yellow Card reports and the scientific literature was considered. There was little new information identified in the literature and limited information to help characterise or identify the causes of these reactions. As there is still no accepted clinical definition for these reactions, not all cases of adverse reactions reported via Yellow Cards as TSW will be true withdrawal reactions. Some of the reported cases may be due to the worsening of the underlying condition or other unidentified causes. However, undoubtedly the review did identify cases of adverse

reactions, often severe, which were associated with the prolonged use of moderate or high potency steroids.

Yellow Card reports up to August 2023 were reviewed and 267 reports were identified reporting reactions under the term TSW or with features that are often considered to be associated with this term. The majority of these reports contain information indicating that the patient experienced a severe reaction following long-term use of moderate to very potent steroids to control eczema.

The most commonly reported reactions include intense itching and burning, cycles of flaking skin, skin exfoliation and skin oozing. The reports also highlighted that the side effects experienced can be severe and patients require support as they can have a high psychological burden[3] (see Joint statement British Association of Dermatologists and National Eczema Society). We have also received a small number of Yellow Card reports that indicate a similar reaction can start whilst topical steroids are still being used. However, overall, the reactions reported to us have been more severe when associated with stopping treatment.

Given the lack of new information in the scientific literature since the previous review, further research is required to fully understand the characteristics and reasons for these reactions.

There are over 11 million prescriptions issued for topical steroids each year.[4] From the data available, TSW reactions are estimated to be rare; however, the reaction frequency cannot be confirmed due to uncertainties regarding under reporting of adverse reactions and the numbers of patient receiving repeat prescriptions. The number of reports of adverse reactions received must be put into context of the millions of people that have benefitted from topical steroid treatment without experiencing any problems.[5]

We have updated our Patient Safety Leaflet for clinicians to use when discussing the risks and advice with patients.

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.

References

1. DermNet. Topical Corticosteroid withdrawal. Accessed May 2024.
2. Tan SY and others. Steroid Phobia: Is There a Basis? A Review of Topical Steroid Safety, Addiction and Withdrawal. Clinical Drug Investigation 2021: volume 41, pages 835 to 842.
3. Brooks TS and others Topical steroid withdrawal: an emerging clinical problem. Clinical and Experimental Dermatology 2023: volume 48, pages 1007 to 1011.
4. Data extracted from ePACT2.
5. Topical Steroid Withdrawal. Joint statement by National Eczema Society, the British Dermatological Nursing Group, and the British Association of Dermatologists. Produced February 2024.

Letters and medicine recalls sent to healthcare professionals in April 2024

National Patient Safety Alert: Reducing risks for transfusion-associated circulatory overload (NatPSA/2024/004/MHRA)

On 4 April, we issued a National Patient Safety Alert to highlight the need to reduce risks for transfusion associated circulatory overload (TACO).

TACO is one of the most common causes of transfusion-related deaths in the UK and cases have increased substantially in recent years. Identifying risk factors for TACO prior to transfusion allows initiation of appropriate mitigating measures.

Letters

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

- Levemir® InnoLet® 100 units/ml solution for injection in pre-filled pen (insulin detemir), Insulatard® InnoLet® 100 international units/ml suspension for injection in pre-filled pen (insulin isophane human), NovoTwist® 5mm needles (32G), NovoFine® 6mm needles (31G), NovoFine® 8mm needles (30G), NovoFine® Autocover® needle (30G) and NovoFine® Remover: DISCONTINUATION
- Sandimmun concentrate for solution for infusion 50mg/ml (ciclosporin): Interim Supply of German Stock to Mitigate Supply Disruption
- Wegovy® 0.5 mg, solution for injection in pre-filled pen (semaglutide): Interim supply of Swiss Stock to Mitigate Supply Disruption

- Mounjaro® ▼(tirzepatide) 2.5 mg KwikPen® solution for injection in pre-filled pen: Extended Use Beyond Printed Expiry Date, Batches D712074, D720751, D720957
- Lanreotide ADVANZ PHARMA 120 mg solution for injection in pre-filled syringe (Lanreotide acetate): Interim Supply of German Stock to Mitigate Supply Disruption
- Adoport (tacrolimus) 0.75mg hard capsules: Interim Supply of Nordic Stock
- Tegretol® 100 mg/5ml Liquid (Carbamazepine): Temporary stock-out and update to posology (reduction of maximum daily dose)

Medicine Recalls and Notifications

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

Class 3 Medicines Recall: Bristol-Myers Squibb Pharmaceuticals Limited, OPDIVO 10 mg/mL concentrate for solution for infusion (nivolumab), EL(24)A/11. Issued 4 April 2024. Bristol-Myers Squibb Pharmaceuticals Limited has informed the MHRA that a potential product quality issue has been detected, relating to incomplete crimping of the metal crimp cap of OPDIVO 10mg/mL concentrate for solution for infusion (nivolumab) (1VLX10ML). Healthcare professionals are advised to stop using the above batches immediately.

Class 3 Medicines Recall: Accord-UK Ltd, Co-Codamol 8/500mg Effervescent Tablets (Key Pharmaceuticals Livery), EL (24)A/12. Issued 10 April 2024. Accord-UK Ltd is recalling a specific batch of Co-Codamol 8/500mg Effervescent Tablets (Key Pharmaceuticals Livery) as a precautionary measure due to the internal tablet blister strips being printed with an incorrect expiry date. Only packs from the specified batch are affected. Healthcare professionals are advised to stop supplying the above batch immediately.

Class 3 Medicines Recall: A. Menarini Farmaceutica Internazionale Srl, Invokana 300mg tablets (Northern Ireland only), EL(24)A/13. Issued on 16 April 2024. A. Menarini Farmaceutica Internazionale Srl is recalling the above batch as a precautionary measure due to the distribution of Invokana 300mg in Northern Ireland in packaging intended for the Greek market. This affects Invokana 300mg (30 tablets) in Northern Ireland only. Healthcare professionals are advised to stop supplying the above batch immediately.

Class 3 Medicines Recall: Neon Healthcare Ltd, Suprefact 1 mg/ml solution for injection (Cheplapharm – Canadian Livery), EL(24)A/14. Issued 23 April 2024. Neon Healthcare Ltd is recalling the specific batch mentioned in this notification as a precautionary measure. This is because the named batch of Suprefact 1mg/ml solution for injection is being distributed in packaging intended for the Canadian market by Cheplapharm, instead of the correct UK packaging. Stop supplying the above batch immediately. Wholesalers are also requested to check stock of Buserelin 1 mg/ml solution for injection for any packs that match Suprefact 1 mg/ml solution for injection (MAH: Cheplapharm – Canadian Livery) as per the product images in the alert.

Medical Device Safety Information

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

0.9% Sodium Chloride Solutions for Irrigation, Inhalation, and Eyewash: recall from manufacturer Legency Remedies, DSI/2024/004. Issued on 4 April 2024. Batches of Legency Remedies Pvt Ltd irrigation, inhalation and eye wash saline products manufactured between April and November 2023 are being recalled due to potential microbiological contamination with Ralstonia pickettii (R. pickettii). For additional information please refer to the Device Safety Information page and the Field Safety Notice.

Symbios ORIGIN® Posterior Stabilised Patient-Matched Total Knee Replacement Device: Risk of Early Revision, DSI/2024/005. Issued 23 April 2024. The MHRA was alerted by Beyond Compliance and the UK National Joint Registry (NJR) to a significantly higher revision rate observed with the ORIGIN PS patient-matched total knee replacement. The ORIGIN PS variant, raised as a level 1 outlier, demonstrates a revision rate (per 100 patient years) that is at least two times higher than all other bicondylar knee replacements in the UK. This issue currently appears to be UK-specific as other international registries do not show the same increase in early revision surgeries.

As a precautionary measure, Symbios Orthopédie SA has initiated a voluntary suspension of all further sales and implantations, alongside a recall of all variants of the ORIGIN device family within the UK. This will be until such a time that further evidence is gathered and assessed. For additional information, please refer to the Device Safety Information page and the Field Safety Notice.

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