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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In our first article this month, we provide information on the risk of topical steroid withdrawal reactions following our comprehensive national review of the evidence. We provide guidance for healthcare professionals about these reactions, as well as advice to be provided to patients and carers on how to reduce the risks of these events.

On page 6 we summarise recent advice relating to COVID-19 vaccines and medicines published since the August 2021 issue of Drug Safety Update. And on page 8 we include recent letters, recalls and notifications sent to healthcare professionals about medicines.

Topical corticosteroids: information on the risk of topical steroid withdrawal reactions

Rarely, severe adverse effects can occur on stopping treatment with topical corticosteroids, often after long-term continuous or inappropriate use of moderate to high potency products. To reduce the risks of these events, prescribe the topical corticosteroid of lowest potency needed and ensure patients know how to use it safely and effectively.

Advice for healthcare professionals:

- long-term continuous or inappropriate use of topical corticosteroids, particularly those of moderate to high potency, can result in the development of rebound flares after stopping treatment – there are reports of such flares taking the form of a dermatitis with intense redness, stinging, and burning that can spread beyond the initial treatment area
- when prescribing a topical corticosteroid, consider the lowest potency needed
- advise patients on the amount of product to be applied; underuse can prolong treatment duration
- inform patients how long they should use a topical corticosteroid, especially on sensitive areas such as the face and genitals
- inform patients to return for medical advice if their skin condition worsens while using topical corticosteroid, and advise them when it would be appropriate to re-treat without a consultation
- for patients currently on long-term topical corticosteroid treatment, consider reducing potency or frequency of application (or both)
- be vigilant for the signs and symptoms of topical steroid withdrawal reactions and review the position statement from the National Eczema Society and British Association of Dermatologists
- report suspected adverse drug reactions to the Yellow Card scheme, including after discontinuation of topical corticosteroids

Advice for healthcare professionals to provide to parents and carers:

- topical corticosteroids are used on the skin to reduce inflammation; when used correctly, they are safe and effective treatments for skin disorders
- always apply topical corticosteroids as instructed and consult the Patient Information Leaflet provided with your medicine
- seek medical advice before using a topical corticosteroid on a new body area as some areas of the body are more prone to side effects
- very infrequent cases of severe skin reactions have been reported in long-term users of topical corticosteroids after they stop using them – see Safety Information Leaflet on topical steroid withdrawal reactions
- if your skin worsens within 2 weeks of stopping a topical corticosteroid, do not start treatment again without consulting your doctor, unless they have previously advised you should do so
- as well as the known side effects associated with using too much of a topical corticosteroid or with using it for too long, remember that using too little can prolong treatment time and increase the risk of certain adverse effects
- ask your prescriber or pharmacist if you have any questions about your medicines or are concerned about side effects – you can also report suspected side effects to the Yellow Card scheme

Background

Topical corticosteroids are safe and highly effective treatments for skin conditions such as eczema, psoriasis, and atopic dermatitis when used correctly. They are available in different potencies:

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

The lowest potency topical corticosteroid for effective treatment should always be used and this may mean using different products for different areas to be treated. The BNF has a guide to potencies using propriety names to help identify the correct preparation.

Review of topical steroid withdrawal reactions

Topical steroid withdrawal reactions have been reported in some long-term users of topical corticosteroids after they stop use.[1,2,3,4] This is a mixed group of symptoms or conditions, often also referred to by patients as ‘red skin syndrome’ or ‘topical steroid addiction’.

1 Hajar T and others. J. Am. Acad. Dermatol 2015; 541-59.

2 Gust P and others. J. Am. Acad. Dermatol 2016; e167.

3 Sheary B. RACGP 2016; 386-88.

4 Sheary B. Dermatitis 2018: 213-18.

A particularly severe type of topical steroid withdrawal reaction, with skin redness and burning worse than the original condition, is currently an under-recognised side effect of topical corticosteroid treatment. Patients report encountering difficulties with diagnosis, leading many to self-treat. However, topical steroid withdrawal reactions are now being recognised by experts in the field and there are treatment options, in addition to alternative treatment approaches for the underlying condition (see position statement from the National Eczema Society and British Association of Dermatologists).

Following concerns from patients and their families about topical steroid withdrawal reactions, the MHRA has conducted a review of the evidence and considered the need for regulatory action to minimise the risk of this side effect. We sought advice on our assessment from the Dermatology and Pharmacovigilance Expert Advisory Groups of the Commission on Human Medicines. Clinical experts in dermatology and representatives from dermatology charities were represented in these discussions.

During our review we considered data gathered from Yellow Card reports and identified 55 reports indicative of topical steroid withdrawal reactions, most of which were reported by patients. We also considered information available in the literature and from other regulators. We are unable to estimate the frequency of these reactions. However, given the number of patients who use topical corticosteroids, we understand reports of severe withdrawal reactions to be very infrequent.

We have made available a Public Assessment Report of this review.

Information about the risks and characteristics of topical steroid withdrawal reactions will be added to the Summaries of Product Characteristics and the Patient Information Leaflets for topical corticosteroid medicines. While the Patient Information Leaflets are being updated, we are supplying an advice for patients on topical steroid withdrawal reactions leaflet for clinicians to use when discussing the risks and advice with patients.

Patient risk factors

Topical steroid withdrawal reactions are thought to occur after prolonged, frequent, or inappropriate use of moderate to high potency topical corticosteroids. Topical steroid withdrawal reactions can develop after application of a topical corticosteroid at least daily for longer than a year.[1,4,5,6] In children they can occur within as little as 2 months of daily use.[5] People with atopic dermatitis are thought to be most at risk of developing topical steroid withdrawal reactions.[1]

5 Juhasz M and others. JDNA 2017: 233-40

6 Rapaport MJ and others. Clin Dermatol 2003: 201-14

It has been reported that the signs and symptoms occur within days to weeks after discontinuation of long-term topical corticosteroid treatment.[5] They are most commonly seen after treatment of sensitive areas such as the face or genitals.

Characteristic signs of topical steroid withdrawal reactions

The most common reaction is a rebound (or flare) of the underlying skin disorder such as atopic dermatitis. However, patients have described a specific type of topical steroid withdrawal reaction in which skin redness extends beyond the initial area of treatment with burning or stinging and that is worse than the original condition. It can be difficult to distinguish a flare up of the skin disorder, which would benefit from further topical steroid treatment, and a topical steroid withdrawal reaction.

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A topical steroid withdrawal reaction should be considered if:

- burning rather than itch is the main symptom
- redness* is confluent rather than patchy (which may not be so obvious in people with darker skin)
- rash resembles atopic dermatitis but involves unusual sites and is ‘different’ to the skin condition that the patient has experienced before
- there has been a history of continuous prolonged use of a moderate or high potency topical corticosteroid

*Redness can be a spectrum of pink, red, and purple, or subtle darkening of the existing skin colour, which can vary depending on the skin tone of the individual.
Skin biopsy is generally unhelpful to distinguish topical steroid withdrawal reactions from a flare of the underlying skin disorder because the histopathology overlaps.

If the patient’s skin condition fails to improve, before prescribing a more potent corticosteroid, consider possible diagnoses such as rosacea, peri-oral dermatitis, infection and allergy to the topical corticosteroid or other topical medications, including moisturisers or cosmetics. Patch testing may identify some cases of contact allergy. If a severe rebound of atopic dermatitis is suspected, review the guidance on alternative treatments.

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.

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.

Article citation: Drug Safety Update volume 15, issue 2: September 2021: 1.

COVID-19 vaccines and medicines: updates for August 2021

Recent information relating to COVID-19 vaccines and medicines that has been published since the August 2021 issue of Drug Safety Update, up to 9 September 2021.

Summaries of Yellow Card reporting and other recent MHRA publications

We continue to publish the summaries 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 will be published regularly to include other safety investigations carried out by the MHRA under the COVID-19 Vaccine Surveillance Strategy.

We have also recently:

- published a statement on booster doses of Pfizer/BioNTech and AstraZeneca COVID-19 vaccines
- given approval to Ronapreve▼ (casirivimab/imdevimab), a monoclonal antibody treatment for the prevention and treatment of COVID-19. For more information about this medicine see the Decision page which includes the Summary of Product Characteristics and Patient Information Leaflet
- updated the shelf life, special precautions for storage and special precautions for disposal in the Summary of Product Characteristics and Patient Information Leaflet for Spikevax (formerly COVID-19 Vaccine Moderna)
- added a precautionary warning about Guillain-Barré Syndrome to the Summary of Product Characteristics and Patient Information Leaflet for Vaxzevria (formerly COVID-19 Vaccine AstraZeneca) following a review of the available data
- authorised an extension to the current UK approval of the Spikevax vaccine (formerly COVID-19 Vaccine Moderna) that allows its use in 12 to 17 year olds

We have previously provided summaries of the latest COVID-19 information, including in the June 2021, July 2021 and August 2021 issues of Drug Safety Update.

See guidance on COVID-19 for all our latest information, including after publication of this article.

Reporting Yellow Cards

Suspected adverse reactions associated with COVID-19 vaccines should be reported to the MHRA through the MHRA's Coronavirus Yellow Card reporting site or via the Yellow Card app.

As these products are under additional monitoring this includes all suspected ADRs 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.

Article citation: Drug Safety Update volume 15, issue 2: September 2021: 2.

Letters and medicine recalls sent to healthcare professionals in August 2021

Letters

In August 2021, the following letters were sent or provided to relevant healthcare professionals:

- Clexane (enoxaparin sodium) device – Important Information regarding differences between PREVENTIS and ERIS needle guard safety systems
- Amiodarone hydrochloride 50 mg/ml concentrate for solution for injection/infusion - potential for crystallisation
- Hizentra Syringe 20% 5ml/10ml (PLGB 15036-0156): interim supply of US Stock to mitigate supply disruption
- Fluenz Tetra nasal spray suspension, Influenza vaccine (live attenuated, nasal): supply of Great Britain-labelled stock in Northern Ireland

Medicine Recalls and Notifications

In August 2021, recalls and notifications for medicines were issued on:

Class 2 Medicines Recall: Various Marketing Authorisation Holders and parallel distributor companies, Irbesartan-containing products, EL (21)A/19. Issued 5 August 2021. Batches of the following medicines are being recalled by multiple manufacturers and distributors: Aprovel 75mg, 150mg and 300mg film-coated tablets, Co-Aprovel 150mg/12.5mg, 300mg/12.5mg Film-Coated Tablets and Irbesartan Zentiva 75mg film-coated tablets. This is a precautionary recall as batches have been identified to contain an impurity of mutagenic potential that is above the acceptable limit. Stop supplying the batches immediately, quarantine all remaining stock and return to supplier. Healthcare professionals should advise patients not to stop taking their medicine without consulting their doctor or pharmacist. The MHRA will provide further updates as our investigation progresses.

Class 2 Medicines Recall: Rosemont Pharmaceuticals Limited, Metformin Hydrochloride 500mg/5ml Oral Solution, EL (21)A/20. Issued 25 August 2021. A batch of Metformin hydrochloride 500mg/5ml oral solution is being recalled as the manufacturer has identified levels of N-nitrosodimethylamine (NDMA) above acceptable limits. As NDMA has genotoxic and carcinogenic potential, this is a precautionary recall. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier. Healthcare professionals should inform patients not to stop treatment without consulting their doctor, as the risk of suddenly stopping this type II diabetes medication is higher than the potential risk associated with the NDMA impurity.

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