Medicines Adverse Reactions Committee

<table>
<tr><td>Meeting date</td><td>13/03/2025</td><td>Agenda item</td><td>3.2.2</td></tr>
<tr><td>Title</td><td colspan="3">Topical steroid withdrawal reactions</td></tr>
<tr><td>Submitted by</td><td>Medsafe Pharmacovigilance Team</td><td>Paper type</td><td>For advice</td></tr>
<tr><td colspan="4">Active ingredient Product name Sponsor
Refer to Table 2</td></tr>
<tr><td>PHARMAC funding</td><td colspan="3"><table><tr><th>Plain corticosteroids</th><th>Corticosteroid combination</th></tr><tr><td>Betamethasone dipropionate
Betamethasone valerate
Clobetasol dipropionate
Clobetasone butyrate
Hydrocortisone
Hydrocortisone butyrate
Methylprednisolone aceponate
Mometasone furoate
Triamcinolone acetonide</td><td>Betamethasone valerate + sodium fusidate
Hydrocortisone + miconazole
Hydrocortisone + natamycin + neomycin
Triamcinolone acetonide + gramicidin + neomycin + nystatin
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<tr><td>Previous MARC meetings</td><td colspan="3">Not discussed.</td></tr>
<tr><td>International action</td><td colspan="3">• MHRA: updates to the product information, package labelling changes, and communication
• Health Canada and Health Sciences Authority (Singapore): communication</td></tr>
<tr><td>Prescriber Update</td><td colspan="3">Steroid Rebound – A Topical Issue (June 2013)</td></tr>
<tr><td>Classification</td><td colspan="3">Pharmacy only medicine, restricted medicine and prescription medicine.</td></tr>
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<tr><td>Advice sought</td><td colspan="3">The Committee is asked to advise:
• On the risk of topical steroid withdrawal reactions and if regulatory action is required to manage the risk?
• If other communication is required, other than in MARC's remarks?</td></tr>
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1 PURPOSE

Topical corticosteroid withdrawal (TSW) reactions, also known as red skin syndrome or topical steroid addiction is a rare rebound reaction reported after stopping long-term use of topical corticosteroids (TCS) products, typically of moderate to high potency.

In 2021, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) reviewed the risk of TSW and implemented risk minimisation measures. These included communicating the risk to healthcare professionals and consumers through updates to summary of product characteristics (SmPC) and patient information leaflets, and publishing an article on TSW reactions in *Drug Safety Update*. More recently, the MHRA announced that TCS products will be labelled with their potency. This is to help patients with correct selection and simplify the advice to patients requiring multiple steroid products of different potencies.

The purpose of this paper is to review the available information on TSW and discuss whether regulatory action is required in New Zealand to manage the risk.

2 BACKGROUND

2.1 Topical corticosteroids

2.1.1 Mechanism of action

Topical corticosteroids are applied to the skin for the treatment of various inflammatory skin conditions (Table 1). TCS have local anti-inflammatory, anti-proliferative and immunosuppressive effects. [1].

Anti-inflammatory effects include vasoconstriction, inhibition of the release of phospholipase A2 and a direct inhibitory effect on DNA and inflammatory transcription factors. The vasoconstriction of blood vessels decreases the number of inflammatory mediators being delivered to the region [1].

Anti-proliferative effects which play a role in the treatment of psoriasis [1].

Immunosuppressive effects involve the inhibition of humoral factors involved in the inflammatory responses, as well as suppression of the maturation, differentiation, and proliferation of all immune cells [1].

Table 1: Common skin conditions managed with topical corticosteroids [2]

TCS are also available in combination products together with a topical antibiotic, antiviral or antifungal. They are used to concurrently treat skin inflammation and the underlying susceptible organism. In addition, TCS is combined with a topical vitamin D analogue (calcipotriol) for the treatment of plaque and scalp psoriasis.

2.1.2 Steroid potency

The potency of a TCS is the amount of medicine needed to produce a desired therapeutic effect [1]. Potency has been historically measured by the intensity of the vasoconstrictive effect. However, the specific molecule, formulation and strength (percentage) also plays a role in the potency [2, 3].

TCS can be grouped according to their potency: 'mild', 'moderate', 'potent' and 'very potent' (Table 2).

Moderate, potent and very potent steroids can be compared to the mildly potent steroid, hydrocortisone [4]:

- Moderately potent steroids are 2-25 times as potent as hydrocortisone.
- Potent steroids are 100-150 times as potent as hydrocortisone.
- Very potent steroids are up to 600 times as potent as hydrocortisone.

Table 2: Approved plain topical corticosteroids grouped based on their potency, according to DermNet and the New Zealand Formulary

Mild	Moderate	Potent	Very potent
Hydrocortisone (0.1-2.5%) DermAid DermAid Soft DermAssist DP-HC Egocort Hydrocortisone (AFT) Hydrocortisone (Ethics) Hydrocortisone (Pharmacy Health) Hydrocortisone (PSM) Hydrocortisone PSM (Noumed) m-Hydrocortisone powder Noumed Hydrocortisone Skincalm Topiderm	**Clobetasone** Eumovate	**Betamethasone valerate and dipropionate** Beta Betnovate Diprosone	**Betamethasone in an optimised vehicle** Diprosone OV
		Diflucortolone* Nerisone	**Clobetasol propionate** Dermol Clobex Clobetasol (BNM)
	Triamcinolone Aristocort	**Mometasone** Arrow-Mometasone Elocon m-Mometasone Mometasone Multichem	
		Methylprednisolone aceponate Advantan	
		Hydrocortisone butyrate Hydrocortisone butyrate (AFT) Locoid	

*no approved products

Comments:

Some resources place methylprednisolone aceponate and hydrocortisone butyrate as a moderate steroid rather than potent.

Potency can also be grouped by the Anatomical Therapeutic Chemical (ATC) Classification. This is based on 'clinical potency':

- Weak (Group I): hydrocortisone
- Moderate (Group II): clobetasone, hydrocortisone butyrate, triamcinolone

- Potent (Group III): betamethasone, diflucortolone, mometasone, methylprednisolone aceponate
- Very potent (Group IV): clobetasol

The above classification does not take into account any additional agents that can enhance the penetration and increase the potency of the product and neither the strength of the preparations nor the vehicle.

It is an important for consumers to note though that a higher strength is not the same as a more potent product.

The US also has their own classification consisting of seven classes, with Class I being super-potent and Class VII being the least potent [1].

The choice of potency of the TCS is generally guided by the patient's age, the type of skin condition, and method of application (eg, whether there will be occlusion) [2].

2.1.3 Adverse effects and duration of use

Adverse effects of TCS can be divided into local and systemic effects.

The proposed mechanism for the local effects of atrophy, tachyphylaxis and striae is highlighted in Table 3. Other local adverse effects include acne, rosacea, hypertrichosis, pigment alteration and delayed wound healing [1].

Table 3: Skin atrophy, tachyphylaxis and striae and their proposed mechanism [1]

Local effect	Mechanism
Skin atrophy	Anti-proliferative effects. Atrophy can occur when there is persistent use in the same region. Areas most at risk for atrophy are intertriginous due to thinner skin and increased occlusion. Atrophy is reversible with cessation of steroid use; however, it may take months for the skin to appear normal again.
Tachyphylaxis	Skin develops tolerance to the TCS, which leads to a loss of vasoconstriction at the level of the capillaries. Capillaries can regain the ability vasoconstrict after 4 days.
Striae	From injury to the dermis and mechanical stress. Inflammation and oedema of the dermis results in collagen deposition in the region of the mechanical stress.

Systemic absorption of TCS can lead to systemic effects such as adrenal suppression. This has been rarely reported but can result in reversible hypothalamic-pituitary-adrenal axis suppression, Cushing's syndrome, and adrenal insufficiency [5].

There are different recommendations for how long TCS should be used to minimise adverse effects.

- A 2009 bpac^{nz} article stated that adverse effects are uncommon when using mild to potent TCS for less than three months, except when used on the face and neck, skin folds, or under occlusion. However, very potent TCS should not be used continuously for longer than three weeks. If longer use of very potent TCS is required, they should be gradually tapered to avoid rebound symptoms and then stopped for a period of at least one week after which treatment can be resumed [6].
- StatPearls (National Library of Medicine) states that the duration of treatment should not be greater than two to four weeks, regardless of potency. High-potency steroids should not be administered for a longer than two weeks, and after this period, should be tapered to avoid adverse effects [1].

    - The New Zealand Formulary states that initial treatment should be generously applied to the affected area once or twice daily to gain rapid control of an inflammatory dermatosis within a few days. After that, a thin smear of topical corticosteroid can be applied no more than once daily until settled. Specialist advice is recommended if potent or very potent topical steroids are required for more than two to four weeks [5].
- The Starship NZ guidelines for outpatient primary management of childhood eczema states that areas which improve but repeatedly flare up require 'maintenance treatment' involving TCS use for two days per week. This type of treatment over 3 to 6 months is safe and effective. Long-term daily use of TCS for many weeks can rarely result in side effects. It is recommended that children using TCS are reviewed regularly and treatment stepped down in frequency, if possible [7].
    - In the 2021 bpac^{nz} article on TCS for childhood eczema, flares should typically resolve within 7 to 14 days. In children who have frequent flares and TCS is effective, maintenance treatment should be considered (see Starship NZ guideline above) [8].
- The Australasian College of Dermatologist consensus is to apply TCS to all inflamed skin until eczema is cleared [9, 10].

Comments:
There are various recommendations for how long TCS should be used continuously. The individual patient's clinical circumstances are likely to play a factor in determining this.

2.2 Topical steroid withdrawal

2.2.1 Reported presentation and stages of TSW

Topical corticosteroid withdrawal describes skin manifestations that develop after stopping long-term use of TCS, typically of moderate to high potency. Before stopping the TCS, the skin often appears normal or near-normal [11].

The cutaneous symptoms reported include burning pain, severe itch, desquamation, oedema, exudate/ooze, and skin sensitivity. Non-cutaneous symptoms include insomnia and depression [12].

Reported signs of TSW include red skin, red sleeve, elephant wrinkles and headlight sign (Figure 1) [12].

Figure 1: Description of TSW signs

The onset of withdrawal symptoms from time of discontinuation ranges from two days to over three months, and typically occurs in four stages [11]:

- The initial stage is an acute eruption of burning red, exudative skin which may extend to untreated areas of the skin.

1. The skin then becomes dry and itchy with desquamation.
2. The skin starts to recover but has increased sensitivity and intermittent flares may occur.
3. The skin recovers to the stage prior to TCS cessation. The recovery process may take weeks to years.

2.2.2 Reported subtypes

Two TSW subtypes have been described (Figure 2) [11]:

Erythematoedematous subtype: commonly seen in patients with chronic atopic dermatitis. This is characterised by burning sensation, erythema, oedema, and scaling.

Papulopustular subtype: commonly seen in patients using TCS for pigmentation changes or other cosmetic reasons. This is characterised by papules, pustules, and erythema. This subtype is less commonly affected by burning, stinging, or swelling.

Figure 2: (A) Erythematoedematous subtype and (B) papulopustular subtype [13]

2.2.3 Risk factors

Major risk factors identified for TSW include [13]:

- Use of TCS on the face
- Use of a medium or high potency TCS
- TCS treatment duration of 6 months or more
- History of atopy, especially atopic dermatitis
- Oral steroid use
- Female gender
- Adults 18 years of age and over.

2.2.4 Diagnosis

The lack of consensus on diagnostic criteria makes identifying cases difficult [11]. A challenge noted is to establish whether the skin reaction observed is due to stopping TCS, the skin condition not adequately treated by the TCS, or worsening of the underlying skin disease for which the steroids were prescribed [14]. This has caused debate by healthcare professionals on whether TSW exists or not, and also apparent differences of opinion between patients and healthcare professionals on this topic. Patients will often self-diagnose themselves and seek help through unregulated online resources [15].

2.2.5 Treatment

There is no consensus for optimal management of TSW in order to reduce the time to resolution. Various treatments have been utilised and this is discussed further in the literature review section of this report [11].

Comments:

TSW is an under-recognised issue which gained recent spotlight in 2021 following MHRA's review. There is significant consumer interest in this issue. It has been reported that from 2016 to 2021 there was a 274% increase in mentions of TSW on social media platforms [16].

In New Zealand, stimulated reporting to the New Zealand Pharmacovigilance Database and media interest appears to have occurred in recent years, coinciding with MHRA's publications.

2.3 Historical information

In May 2021, Medsafe received a case report (CARM ID 140982) describing a 4-year old male who had received 1% hydrocortisone topically once or twice daily for 10 weeks for eczema. After stopping the

treatment for 24 hours, the eczema rash returned and new rashes around eyes and mouth were noted. The skin became extra sensitive to any creams and water which was normally tolerated well. The child's caregiver decided to stop steroid use and from then the rashes improved with time (this contravened the advice given by their GP which was to continue with TCS as this was the only way to manage the eczema). The child developed red sleeves and initially the skin was oozy and swollen which improved with time.

The child was subsequently underwent allergy testing and was found to be allergic to tree nuts.

This case prompted Medsafe to review if such reactions were described in the data sheet. The Beta ointment data sheet had the following information:

> *4.2 Dose and method of administration*
>
> *Rebound of pre-existing dermatoses can occur with abrupt discontinuation of topical corticosteroid preparations.*
>
> *4.8 Undesirable effects*
>
> *General disorders and administration site conditions – "Rebound effect"*

Medsafe subsequently requested updates to all data sheets containing a TCS with the above information.

Comments:

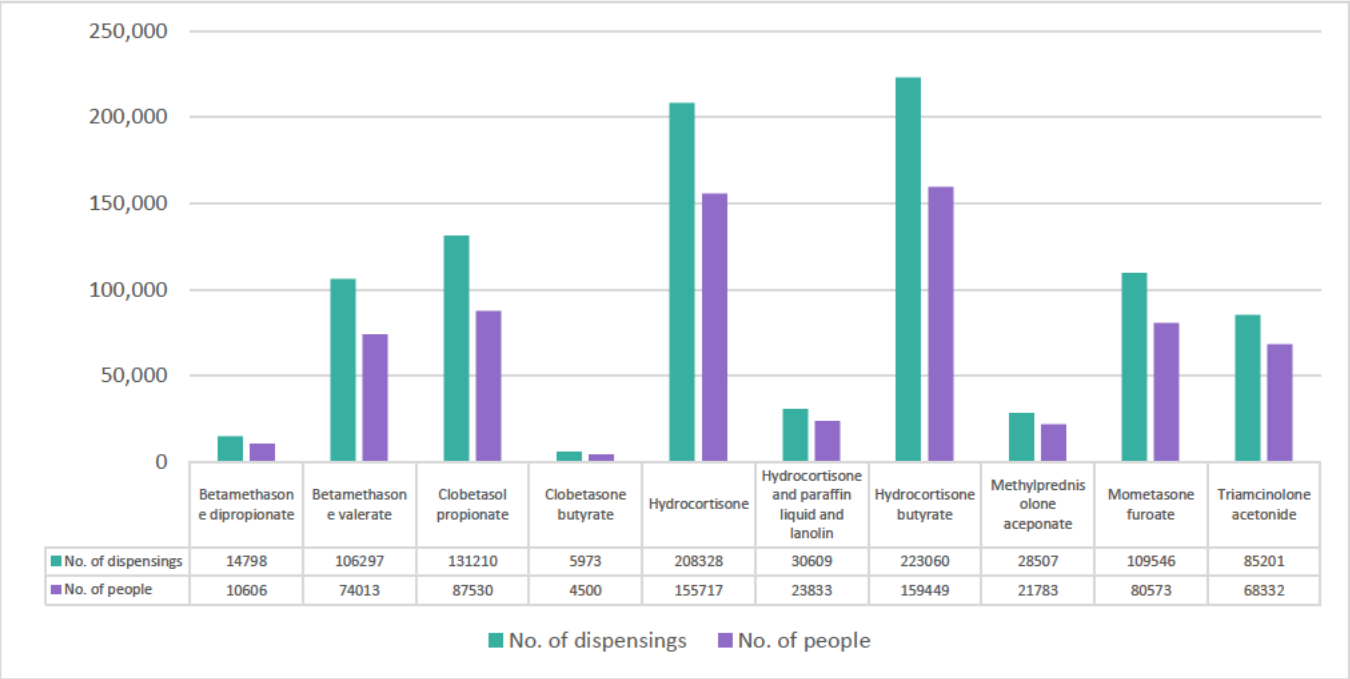
Not all sponsors agreed to update their data sheets. Some sponsors argued that as TSW typically occurs from long-term inappropriate use, it is unlikely to occur with normal application of TCS as indicated in the data sheet.

The term 'rebound effect' was appropriate at the time to describe the reaction as the term TSW was not widely used or seen in international product information. However, using 'rebound effect' today may not fully capture other aspects of TSW, such as the intense redness, stinging and burning that can extend beyond the initial treatment area that occurs after stopping TCS.

2.4 Usage

Figures 3 and 4 show plain corticosteroid usage data by number of dispensings and the number of people being prescribed, for the years 2022 and 2023 respectively. Hydrocortisone (mild potency steroid) and hydrocortisone butyrate (potent steroid) were the most used plain TCS.

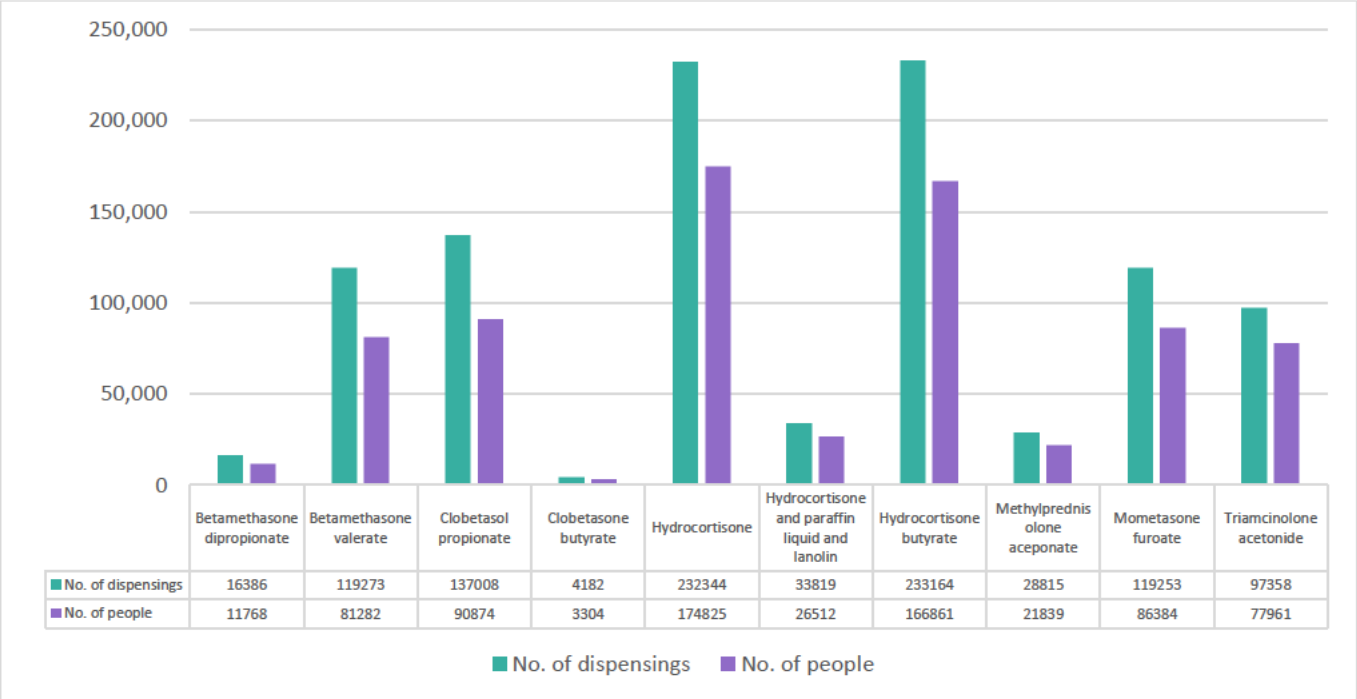
Figure 3: Plain topical corticosteroid usage data, by chemical in 2022



	Betamethasone dipropionate	Betamethasone valerate	Clobetasol propionate	Clobetasone butyrate	Hydrocortisone	Hydrocortisone and paraffin liquid and lanolin	Hydrocortisone butyrate	Methylprednisolone aceponate	Mometasone furoate	Triamcinolone acetonide
No. of dispensings	14798	106297	131210	5973	208328	30609	223060	28507	109546	85201
No. of people	10606	74013	87530	4500	155717	23833	159449	21783	80573	68332

Source: Health New Zealand Pharmaceutical Data web tool: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 19 February 2025)

Figure 4: Plain topical corticosteroid usage data, by chemical in 2023



	Betamethasone dipropionate	Betamethasone valerate	Clobetasol propionate	Clobetasone butyrate	Hydrocortisone	Hydrocortisone and paraffin liquid and lanolin	Hydrocortisone butyrate	Methylprednisolone aceponate	Mometasone furoate	Triamcinolone acetonide
No. of dispensings	16386	119273	137008	4182	232344	33819	233164	28815	119253	97358
No. of people	11768	81282	90874	3304	174825	26512	166861	21839	86384	77961

Source: Health New Zealand Pharmaceutical Data web tool: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 19 February 2025)

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Sheary 2019 – Topical steroid withdrawal: A case series of 10 children [17]

This case series examined the histories of ten children between the ages from 8 months to 15 years presenting with TSW in an Australian general practice (Table 4). The children had all been using TCS over months to years which had then been stopped by their parents.

Table 4: Characteristics of the children in the case series

In general, the majority of cases involved children using TCS for atopic dermatitis (80%) applied to the face (80%), and most children were females (70%). All cases reported increase of the amount and potency of TCS used over time.

Most cases (80%) presented with diffusely red skin, and either 'elephant wrinkles' or 'red sleeve' (or both). Some cases presented with complaints appearing similar to their original skin condition whilst other cases developed complaints in areas not confined to the originally affected area of their skin (Table 5).

Table 5: Characteristic signs of topical steroid withdrawal, complications and management strategies of cases

While TSW was considered the most likely diagnosis in these children, confirmation was not possible as diagnostic criteria did not exist when they were first assessed, and due to the inability to completely exclude all differential diagnoses (eg, allergic dermatitis). A flare of the children's underlying condition could also have been possible.

The author noted that the most common reason for withdrawing TCS was the concern of TSW. Only two children stopped their TCS because it was no longer effective. There was a lack of management guidelines and treatment included supportive care and alternative medicine.

The author emphasised that further research into TSW is needed to establish a consensus diagnostic criteria and evidence-based management guidelines.

3.1.2 Hajar et al 2015 - A systematic review of topical corticosteroid withdrawal ("steroid addiction") in patients with atopic dermatitis and other dermatoses [13]

A systematic review of the literature was conducted to better define TSW, the signs/symptoms and potential risk factors.

A total of 192 articles were identified (containing 1,085 patients). All evidence was ranked as very low quality (Level 4 ranked according to the GRADE guidelines). The majority of patients were women (81%) who used TCS on their face (97%). A third of the patients were using TCS for atopic dermatitis.

Of the patients that developed TSW reactions, 98.6% were using either a mid or high-potency steroid.

Duration of use was reported in 14 studies (consisting of 210 patients) and 85.2% of those patients reported to have used TCS for more than 12 months.

Table 6 outlines the onset of TSW symptoms, and the signs and symptoms reported. Burning/stinging, followed by exacerbation when exposed to heat/sun and pruritis were the most common symptoms suggestive of TSW. The most commonly reported signs were erythema, papules and pustules.

The most frequently reported time to onset was between 2-3 weeks (66.2%).

Table 6: Clinical features of topical steroid withdrawal

No effective management strategy was reported. The most commonly reported measures were discontinuation of the TCS (n=681, 95.5%), oral antibiotics (n=240, 33.6%), antihistamines (n=151, 21.1%), and supportive measures such as psychological support and ice/cool compress.

A diagnosis of TSW was noted to be challenging to make as it could overlap with other clinical presentations such as contact dermatitis (patch testing could be useful to exclude this), a flare up of the underlying dermatosis or skin infection.

The authors state that care should be taken by healthcare professionals since confusing the signs and symptoms of atopic dermatitis for steroid withdrawal could lead to unnecessary withholding of necessary TCS therapy. Healthcare professionals should favour a diagnosis of topical steroid withdrawal over a flare-up of the underlying atopic dermatitis if the following features are present:

- burning is the prominent symptom,
- confluent erythema occurs within days to weeks of topical corticosteroid discontinuation, and
    - a history of frequent, prolonged topical corticosteroid use on the face or genital region.

Overall, the authors considered that TSW is likely a clinical adverse effect distinct from other well-described adverse effects from TCS. TSW generally occurs with the inappropriate prolonged frequent use of high-potency TCS. There is low quality of evidence in the literature and no agreed diagnosis criteria or treatment guidelines. Well-designed, prospective studies with rigorous methodology are needed to better understand and define this condition.

3.1.3 Hwang et al 2022 – Topical corticosteroid withdrawal ('steroid addiction'): an update [18]

This systematic review builds on Hajar's 2015 systematic review above.

Eleven additional studies were identified describing TSW: two cross-sectional studies, two case series and seven case reports.

The clinical features of the TSW cases are summarised in Table 7 panels A-B and the time to onset and treatment for TSW (outcome of treatment not known) is summarised in panel C.

Table 7: (A) Patient and steroid characteristics, (B) Clinical features, (C) Time to onset and treatment

[redacted]

(C)

[redacted]

The authors conclude that their updated systematic review reinforces the findings seen in the earlier systematic review by Hajar: that the reaction usually occurs after prolonged, inappropriate and frequent use of TCS. Patient education including elements such as risks of prolonged use beyond instructed time, and the need to follow up treatment are important factors to address improper usage.

3.1.4 Sheary 2018 – Steroid withdrawal effects following long-term topical corticosteroid use [12]

This retrospective cohort study examined the demographics and outcome in adult patients with suspected TSW in an Australian general practice between 2015 and 2018.

Sixty-nine patients with TSW were identified. Most cases were female (56%) aged 25-34 years (42%) who were using a potent TCS (60%) for atopic dermatitis (76%) on the face (84%).

Many of the symptoms seen in TSW may also be seen in severe atopic dermatitis; however, others were more typical of TSW and were thus helpful in differentiating between the two diagnoses. Burning pain was reported in 65%; excessive skin desquamation in 75%; swelling in 65%; and skin sensitivity in 47% of cases. Signs that have been reported commonly (but not necessarily exclusively) in TSW were seen in a number of patients: diffusely red skin in 100%; elephant wrinkles in 56%; red sleeve in 40%; and the headlight sign in 29%.

Although there were no diagnostic criteria for TSW, the author proposed suggested diagnostic criteria as a point for discussion and future research (Table 8).

Table 8: Suggested diagnostic criteria for TSW - a starting point for discussion and future research

3.1.5 Brookes et al 2023 – Topical steroid withdrawal: an emerging clinical problem [19]

A retrospective review of case notes collected from a multidisciplinary service was carried out to identify patients presenting with TSW. Nineteen cases were identified between 2019 and 2021. The majority of cases were female (79%) with a mean age of 31 years (age range 3 to 62 years).

The TCS potency was documented in 13 cases and in 12 of those mild/high potency TCS was used. Twelve cases reported they had used TCS for more than 3 months.

Of the total cases, 18 had a primary skin diagnosis of atopic dermatitis that was typically severe at the time of presentation. However, 10 reported clearance of their skin prior to onset of TSW. All cases had been treated with TCS for prolonged periods (from 3 months to 15 years) prior to experiencing TSW.

Nearly all cases experienced skin redness, pain, sensitivity, excessive exfoliation/flaking/shedding, and insomnia. There was a high burden of anxiety, depression and suicidal thoughts in this group.

Early improvements of TSW symptoms were noted in patients treated with conventional treatment as part of their management. The authors utilised a combination of treatments such as low-dose antibiotics, antihistamines, topical calcineurin inhibitors, gabapentin and emollients as conventional treatment, depending on symptoms and preference.

The authors also noted it was common for patients to share their experiences online of symptoms being dismissed by healthcare professional and therefore seeking non-conventional management. Approximately half of the cases had pursued non-conventional treatment for TSW which included complimentary medicine, acupuncture, traditional Chinese medicine and overseas dermatology professionals who were considered experts in TSW.

3.1.6 Feschuk et al 2023 – Topical steroid withdrawal syndrome in a mother and son: a case report [20]

This case report describes a mother and son with atopic dermatitis.

The mother had a long-standing use of desonide and betamethasone dipropionate daily for 13 years. Her son used the same treatment for the last five years.

During the 5-year overlap, the mother and son collectively went through 360 grams and 210 grams of the TCS respectively in approximately two months.

In 2020, the mother and son were required to do a 2-week public health isolation period related to COVID-19, during which they ran out of TCS. They presented to the hospital with erythema, severe burning/stinging, and swelling/oedema. Others in the household who were required to isolate and had not used TCS did not experience the same issue.

Both patients were diagnosed with TSW and treatment included TCS discontinuation and psychological support. Throughout their recovery, they had widespread skin involvement affecting the face, neck, back, flexural surface and limbs.

After being TCS free for two years, their skin has much improved.

The authors suggest this case study supports that TSW as its own entity as both patients had the same time to onset and improved when they discontinued TCS.

3.1.7 Barlow et al 2024 – Topical steroid withdrawal: a survey of UK dermatologists' attitudes [21]

The authors conducted a survey among members of the British Association of Dermatologists on their knowledge and attitudes on TSW. Among the 121 respondents (a low response rate of only 5.9%), the majority considered that in most cases, patients complaining of TSW were simply experiencing eczema that relapsed because their TCS was stopped (74 respondents, 61.2%). The majority agreed that more research into TSW was needed (n=107, 88.4%) and on the long-term safety of TCS (n=92, 76.0%). Only 14 (11.6%) felt very confident in addressing patient concerns around TSW, with 60 (49.6%) moderately confident and 47 (38.8%) not so confident.

A total of 88.4% (n=107) agreed that TSW needs better understanding and more research. This will enable a definition of TSW, a diagnostic criteria and treatment.

Comments on the literature review:

TSW is noted to be mainly consumer-reported. There is growing literature on TSW from systematic reviews and case series. The quality of the available evidence at the current time is low. TSW is not well-defined making diagnosis and treatment difficult.

Some papers note that there are features of TSW that are clinically distinct from a rebound of the person's underlying skin disease. Some distinctive features described include [22]:

- spread of rash and redness to new areas of the skin beyond the initial treatment area
- shift from itching to burning or stinging of skin, and
- confluent skin redness rather than patchy (more flushed skin similar to a sunburn).

There is a lack of shared understanding among consumers and healthcare professionals about what constitutes TSW. This has caused an attitude of distrust from consumers towards their healthcare professionals. There is also scepticism on the existence of this disease from healthcare professionals and this has also led to steroid phobia. Nevertheless, healthcare professionals agree that more research and understanding is needed to better diagnose and treat the condition.

3.2 Position statements and guidelines

3.2.1 American Academy of Dermatology guidelines [23]

The guidelines on management of adult atopic dermatitis with topical therapies state that the adverse effects of topical steroid addiction (TSA) and TSW are less clearly characterised in the literature. Recent systematic reviews analysed published case series and reports and deemed the strength of the evidence to be very low. The most consistent risk factor associated with TSA/TSW is prolonged, inappropriate use of potent topical steroids on the face or in intertriginous areas, which would be inadvisable in any case. Red face syndrome and red scrotum syndrome, characterized by persistent redness of the face and scrotum respectively, may occur after prolonged use of TCS.

3.2.2 Joint statement from the British Association of Dermatologists, British Dermatological Nursing Group, and the National Eczema Society [24]

An updated joint statement was released in 2024 on TSW. The following points were conveyed:

- TCS are safe and effective for many people. Most side-effects are well known, often this means there is good enough research to understand and manage them.
- The group of side effects known as TSW are generally less well understood.
- Recently there have been increased awareness of TSW, in part of people sharing their experiences on social media.
- The UK regulator has reviewed TSW and as a result now including a warning.
- Despite this, there remain many challenges to understanding and managing TSW. The term has been used to describe a range of issues, some of which are already recognised side effects of topical steroids.
- The lack of a clear medical definition can make it difficult for healthcare professionals to communicate with people who are experiencing these reactions. It also means that some people who think they have TSW may be experiencing another condition.
- There has been very little research on the topic. This means that information is based on patient reports and the opinions of healthcare professionals. These are important and useful but do not give us the full picture. More good quality research would make it easier to understand how common these problems are, what causes them and how to manage them.
- Despite the lack of research, we would encourage healthcare professionals to be supportive of patients living with symptoms of TSW. Trying to find common ground and agree on practical plans for treatment will help patients who have concerns about the use of topical steroids.

3.2.3 New Zealand Formulary [5]

The NZF has information on TSW reactions:

Topical steroid withdrawal reactions

Withdrawal reactions (which may appear as symptom rebound or flare) can occur in the days or weeks following cessation of long-term topical treatment with corticosteroids, or following inappropriately frequent use of *moderate* to *high potency* products (especially on the face or genital area). Withdrawal reactions are thought to occur rarely and can produce dermatitis with intense redness, stinging, and burning that extends beyond the initial symptomatic area (especially in those with eczema). Monitor individuals for the development of these symptoms following discontinuation of long-term treatment. Ideally topical corticosteroids should be discontinued gradually, with ongoing regular emollient use to repair and protect the natural skin barrier. If previous discontinuation of a topical steroid was associated with a reaction that raises suspicion of a topical steroid withdrawal reaction, alternative treatments could be considered.

The least potent topical corticosteroid that is effective should be used and individuals should be advised to carefully follow instructions regarding the frequency, location (ensure correct potency for each body area), and duration of use.

3.2.4 The National Eczema Association in the US [25]

The National Eczema Association has recognised TSW as a serious potential side effect of TCS:

> *National Eczema Association is committed to raising awareness about Topical Steroid Withdrawal (TSW), a serious potential side effect of topical steroid use that is not readily recognized by patients and providers. Much is still unknown about this condition, most notably how often it happens and the amount of topical steroid use that causes it to occur. While we believe topical steroids have a role to play in the management of eczema, it's important for the eczema community to be aware of TSW. Many people with similar conditions, such as papulopustular, rosacea and psoriasis use topical steroids for management and should be aware of TSW as well.*

3.3 Spontaneous reports

3.3.1 New Zealand reports

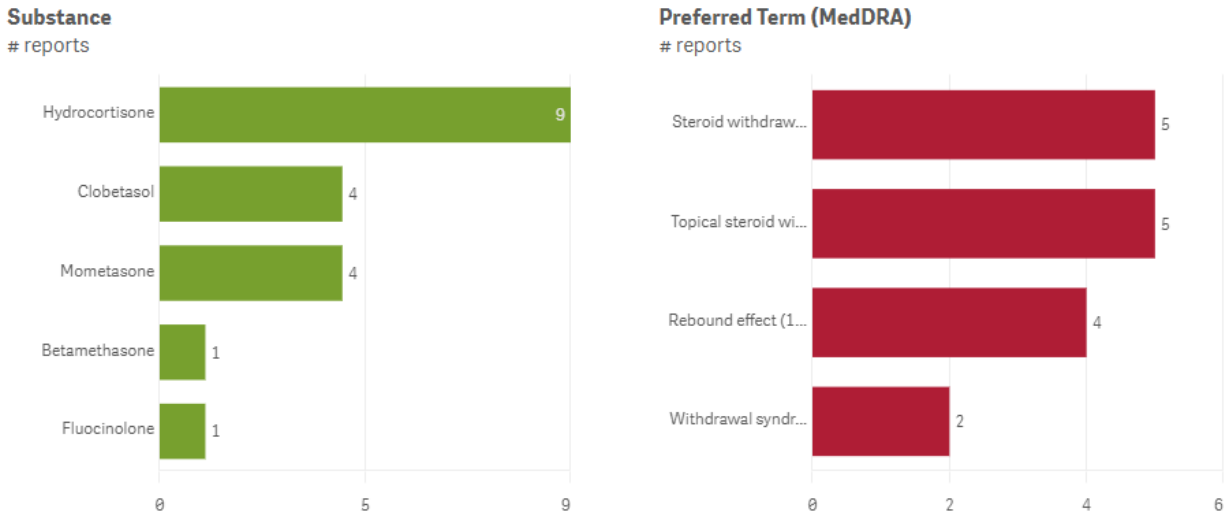
Up to 31 January 2025, there have been 16 cases reporting *'rebound effect'*, *'steroid withdrawal reaction'*, *'steroid withdrawal syndrome'*, *'topical steroid withdrawal'* or *'withdrawal syndrome'* with the use of TCS.

A summary of trends is displayed in Figure 5

Case summaries are outlined in Table 9.

Figure 5: Overview of the 16 cases involving possible topical steroid withdrawal up to 31 January 2025

[redacted]



Source: Qlik Suspected adverse reactions to medicines (accessed 14 February 2025).

Table 9: Case summaries of topical steroid withdrawal reported in New Zealand

Case number	Reporter type	Age and sex	Suspect(s) (potency)	Duration of use	Reactions terms	Narrative
NZ-Medsafe-160059	[redacted]	30-yo-M	Betamethasone valerate cream (potent)	[redacted]	Inflammation Infection Withdrawal syndrome	[redacted]
NZ-Medsafe-159519	[redacted]	Not reported	Hydrocortisone*	[redacted]	Topical steroid withdrawal	[redacted]
NZ-Medsafe-159502	[redacted]	31-yo-F	Mometasone furoate (potent)	[redacted]	Topical steroid withdrawal	[redacted]
NZ-Medsafe-159500	[redacted]	24-yo-M	Hydrocortisone*	[redacted]	Topical steroid withdrawal	[redacted]
NZ-Medsafe-152781	[redacted]	9-yo-M	Mometasone furoate (potent) Betamethasone (potent)	[redacted]	Skin burning sensation Itchy skin Steroid withdrawal syndrome	[redacted]
NZ-Medsafe-155591	[redacted]	33-yo-F	Clobetasol propionate (very potent) [redacted] Hydrocortisone butyrate cream (potent) [redacted]	[redacted]	Topical steroid withdrawal reaction	[redacted]

			Hydrocortisone butyrate scalp lotion (potent) [redacted]			
NZ-Medsafe-156891	[redacted]	32-yo-F	Clobetasol propionate (very potent)	[redacted]	Topical steroid withdrawal reaction	[redacted]
053393	[redacted]	30-yo-F	Fluocinolone (potent)	[redacted]	Rosacea Withdrawal syndrome	[redacted]
105640	[redacted]	22-yo-M	0.5% hydrocortisone cream (mild)		Rebound effect	[redacted]
107985	[redacted]	18-yo-F	Hydrocortisone butyrate cream (potent) Hydrocortisone (mild) Prednisone (systemic)	[redacted]	Rebound effect Application site dermatitis	[redacted]
108144	[redacted]	24-yo-F	Hydrocortisone butyrate cream (potent)	[redacted]	Steroid withdrawal syndrome Eczema aggravated	[redacted]

			Clobetasol propionate (very potent) Prednisone (systemic)			
108342		18-yo-M	Mild steroid, hydrocortisone butyrate (potent), clobetasol propionate (very potent)		Drug dependence Rebound effect	
140479		37-yo-F	Mometasone furoate (potent) Clobetasol (very potent)		Steroid withdrawal syndrome Pruritis Secondary immunodeficiency Erythema Application site exfoliation	
140982		4-yo-M	Hydrocortisone*		Rebound effect	
142209		28-yo-F	Hydrocortisone* Prednisone (systemic)		Steroid withdrawal syndrome	
143187		5-month old-F	Hydrocortisone* Mometasone (potent) Methylprednisolone (potent)		Steroid withdrawal syndrome Medication error	

Note:

*Unknown if hydrocortisone used was the mild potency or potent version (hydrocortisone butyrate).

Comments:

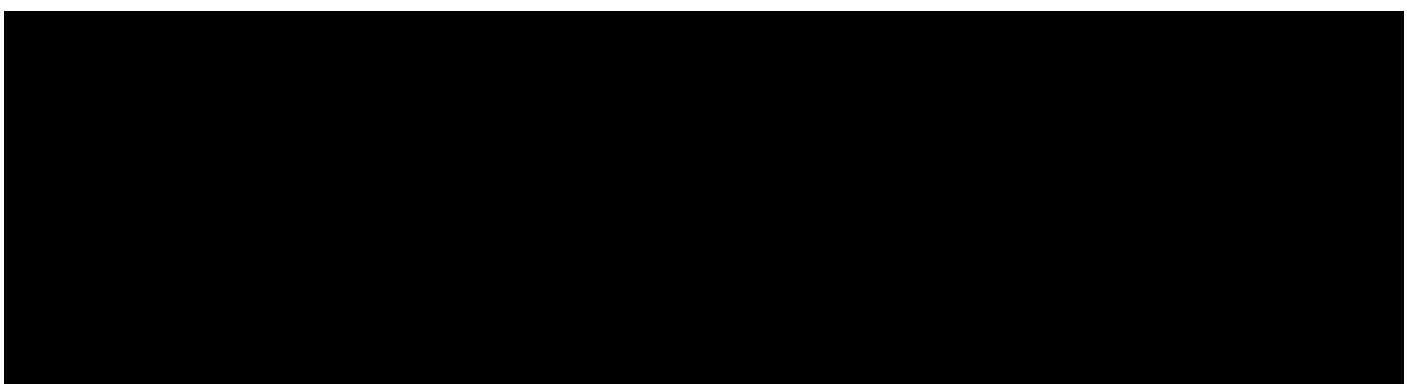
The search terms used were specific. There are possibly more cases if non-specific symptoms like red skin, burning, itching are used.

11 out of the 16 reports were made after 2021, coinciding with the highly publicised MHRA's review.

The most frequently reported TCS was hydrocortisone in 9 reports (although this number might include both the mild and potent steroid), followed by clobetasol (4) and mometasone (4).

Most cases concerned females (9) over 18 years of age (11). This reflects the demographics reported in the literature.

[redacted]



[redacted]

[redacted]

3.4 International review and action

Publicly available information is summarised below:

3.4.1 Medicines and Healthcare products Regulatory Agency

In 2021, the MHRA published their review of the evidence for TSW [26].

The MHRA has received 55 reports in their spontaneous reporting database of probable cases of TSW and 62 further cases potentially indicative of TSW. The cases have been reported over a wide time-period, and the majority of reports were from patients.

Many of the reports received had the recurring theme that patients found the information on TSW reactions for themselves rather than receiving a diagnosis from a healthcare professional.

The literature review suggested that TSW reactions are thought to result from prolonged, frequent, and inappropriate use of moderate to high-potency topical corticosteroids. It has been reported that these reactions develop after application of a topical steroid at least daily for more than a year. To date, they have not been reported with normal use, such as treating certain skin conditions for short periods of time, or with short breaks in treatment over an extended period. People with atopic dermatitis are thought to be most at risk of developing TSW. The signs and symptoms occur within days to weeks after discontinuation of long-term TCS treatment.

Many of the symptoms associated with TSW reactions are listed individually within the patient information leaflets for TCS. These include inflammation and/or infection of the hair follicles, thinning of the skin, red marks with associated prickly heat, loss of skin colour, burning, stinging, itching or tingling.

The MHRA has taken the following actions:

- Requesting updates to the product information and patient information leaflets. Even though the current product information for TCS may list some of the individual symptoms of TSW, there was no mention of reactions occurring after stopping treatment. The MHRA considered an update was appropriate to better reflect the possible reactions that can be experienced.
- Publishing a *Drug Safety Update* communication. This communication outlined the MHRA's review of TSW and provided the following advice for healthcare professionals:
    - 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.
- Introducing labelling requirements for the packaging of TCS to include their potency. Although not directly related to TSW, this will aid in correct selection and simplify the advice to patients requiring multiple steroid potencies. Products will be labelled 'mild steroid', 'moderate steroid', 'strong steroid', or 'very strong steroid' [27].

3.4.2 Health Canada [22]:

In July 2022, TSW was communicated in Health Canada's Health *Product InfoWatch*. No specific action was taken by the Agency but to continue monitoring.

The Agency highlighted the following measures to prevent TSW:

- Prescribe the lowest potency needed.
- Advise patients on the amount and frequency of application.
- Inform patients on the duration of use, particularly on sensitive areas (eg, face and genitals).
- Switch to a lower potency TCS if treatment is beyond the recommended duration of the time is necessary.
- Taper use or advise periodic breaks in treatment in patients on long-term, continuous TCS treatment.
- Inform patients to seek medical advice if their skin conditions worsen while using TCS or within 2 weeks after stopping treatment.

3.4.3 Health Sciences Authority (Singapore) [28]:

A safety alert was published in 2022. The following points were conveyed:

- Recognition and diagnosis of TSW remains a challenge.
- The reviews concluded that TSW is likely a distinct clinical adverse effect resulting from prolonged, inappropriate, and frequent use of moderate- to high-potency TCS. However, the reviewed evidence (i.e., observational studies) was of low quality and at risk of bias, necessitating further well-designed studies to better understand and define this entity.
- As the Health Sciences Authority (HSA) continues to monitor reports of TSW with the use of TCS, healthcare professionals are advised to take into consideration the above information when prescribing TCS, and to consider the possibility of TSW in patients with a history of continuous prolonged TCS use who present with suggestive clinical signs. Healthcare professionals are also encouraged to report to HSA any suspected cases of TSW related to the use of TCS.

[redacted]

[redacted]

3.6 Data sheets and Consumer Medicine Information (CMI)

3.6.1 New Zealand (for plain TCS)

The data sheets for each TCS innovator (or the funded product if the innovator is not available) were reviewed (Table 10) for information on rebound effect, TSW, potency information and whether the indication/warning suggest that the product should not be used long-term continuously.

The CMI and package labelling were to see if the potency was stated.

- Boxes shaded in red indicate there is no information in the data sheet/CMI.
- Boxes shaded in green indicate there is information in the data sheet/CMI.
- Boxes shaded in yellow indicate the potency is mentioned but only as part of the ATC classification.

Table 10: Review of plain topical corticosteroid data sheets, CMI and package labelling

TCS (sponsor), potency	Rebound effect	Indication or warnings suggesting the TCS should not be used long-term/has a maximum duration of continuous use	Mention of TSW/RSS	List signs/symptoms of TSW?*	Potency mentioned in data sheet?	Potency mentioned in the CMI?	Potency mentioned on the package labelling?
Diprosone OV, (Organon) Very potent					Says it is a 'potent' steroid		
Dermol (Viatris) Very potent		Yes, for children and elderly			Yes in 5.1**		
Beta (Viatris) Potent					Yes in 5.1**		
Diprosone (Viatris) Potent					Yes in 5.1**		
Elocon (Organon) Potent		Paediatric warning only					
Advantan (Leo) Potent					Yes in 5.1**		
Locoid (Link Pharmaceuticals) Potent		Paediatric warning only					
Eumovate (GSK) Moderate					Yes in 5.1**		
Aristocort (Pharmacy Retailing t/a HCL) Moderate		Paediatric warning only					
DermAid (Douglas) Weak					Yes in 5.1**	CMI not found	
DP Lotion-HC (Douglas) Weak					Yes in 5.1**		
Hydrocortisone 1% cream Ethics (Multichem) Weak					Yes in 5.1**	CMI not found	
Hydrocortisone 1% cream (AFT) Weak						CMI not found	
Hydrocortisone 1% cream (Noumed) Weak							
Topiderm 1% cream (AFT) Weak					Yes in 5.1**	CMI not found	

*may include skin redness/erythema, burning, flaking/dryness, pruritis and oozing

**Potency stated in section 5.1 as part of its ATC classification naming.

Comments:

Only the Dermol cream/ointment data sheet contains a warning on TSW:

Section 4.4: **Topical steroid withdrawal syndrome**

> *Long term continuous or inappropriate use of topical steroids can result in the development of rebound flares after stopping treatment (topical steroid withdrawal syndrome). A severe form of rebound flare can develop which takes the form of a dermatitis with intense redness, stinging and burning that can spread beyond the initial treatment area. It is more likely to occur when delicate skin sites such as the face and flexures are treated.*
>
> *Should there be a reoccurrence of the condition within days to weeks after successful treatment a withdrawal reaction should be suspected. Reapplication should be with caution and specialist advise is recommended in these cases or other treatment options should be considered.*

The Dermol cream/ointment CMI has the following:

Tell your doctor as soon as possible if you notice any of the following effects…

- *After long term continuous use rebound flares can occur after stopping treatment (topical steroid withdrawal syndrome). A severe form of rebound flare can develop which takes the form of a dermatitis with intense redness, stinging, burning, itch, skin peeling, oozing pustules that can spread beyond the initial treatment area. It is more likely to occur when delicate skin sites such as the face and flexures are treated. Should there be a reoccurrence of the condition within days to weeks after successful treatment a withdrawal reaction should be suspected. Reapplication should be with caution and specialist advise is recommended in these cases or other treatment options should be discussed with your doctor.*

Interestingly, Dermol scalp lotion (having same active ingredient as the cream/ointment) does not have a warning despite the product being sponsored by the same company. The scalp lotion is indicated for psoriasis and eczema.

The data sheets for other plain TCS list non-specific symptoms of TSW such as burning skin, redness, itching and dryness.

Most data sheets have rebound effect listed, as requested previously by Medsafe:

> *Rebound of pre-existing dermatoses can occur with abrupt discontinuation of topical corticosteroid preparations.*

Review of the indication/warnings in the data sheet showed that most potent and very potent steroids have information that their product should not be used long-term continuously. This is generally expressed as:

- having a usual maximum duration of application (ranging from 4-12 weeks) and if using beyond this period, to reduce the frequency of application or to change treatment to a less potent preparation afterwards.
- Apply until improvement then reduce frequency of application.

Most data sheets mention the potency in section 5.1, as part of declaring the ATC code in the data sheet.

No package labelling had information on the steroid potency. Some CMI stated the potency under the heading '*What is [drug name] used for?*'.

3.6.2 International

3.6.2.1 United Kingdom

Most TCS have the following warning and ADR in the data sheet, in addition to text about the risk of rebound effect after sudden discontinuation of TCS.

> Section 4.4
>
> Long term use of topical steroids can result in the development of rebound flares after stopping treatment (topical steroid withdrawal syndrome). A severe form of rebound flare can develop which takes the form of a dermatitis with intense redness, stinging and burning that can spread beyond the initial treatment area. It

is more likely to occur when delicate skin sites such as the face and flexures are treated. Should there be a reoccurrence of the condition within days to weeks after successful treatment a withdrawal reaction should be suspected. Reapplication should be with caution and specialist advise is recommended in these cases or other treatment options should be considered.

Section 4.8

Withdrawal reactions – redness of the skin which may extend to areas beyond the initial affected area, burning or stinging sensation, itch, skin peeling, oozing pustules (see section 4.4).

Frequency: Not known

Australian

The product information in Australia does not list TSW.

4 RISK MINIMISATION MEASURES

Risk minimisation measures are actions that could be taken to reduce the likelihood of adverse events from occurring or lessen their impact. The MARC could consider the following measures:

4.1 Updates to the data sheet

Topical steroid withdrawal

The Dermol ointment/cream data sheet has information on TCS in sections 4.4 and 4.8. The MARC could advise Medsafe to request the sponsors of all TCS (or TCS of certain potencies) to update their data sheet with similar information. However, in 2021 many sponsors indicated no updates to include TSW reactions are planned given the limited available evidence at the time and that TSW typically occurs from long-term inappropriate use which is unlikely to occur with normal application of TCS as indicated in the data sheet. Given the argument that TSW reactions have occurred from long-term and inappropriate use of TCS, it may be appropriate to have information on TSW reactions in the overdose section of the data sheet (section 4.9).

Duration of continuous use

Duration of use appears to be a risk factor for TSW reactions and most TCS data sheets have information on a maximum duration of continuous use (see Table 11). In general, the data sheets contain one or more of the following information suggesting TCS should not be used long-term continuously:

- A defined maximum duration of continuous use, and if using beyond this period, to reduce the frequency of application or change to a less potent preparation,
- Long-term continuous use should be avoided where possible,
- Informing the patient to seek further healthcare professional advice if the symptoms does not resolve in [x] number of days.

Table 11: TCS data sheets and wording suggesting the product should not be used long-term continuously

TCS (sponsor), potency	Data sheet wording
Diprosone OV, (Organon) Very potent	Section 4.4 As with all highly active topical corticosteroid preparations, treatment should be discontinued when the dermatological disorder is controlled. According to clinical response, duration of therapy may vary from a few days to a longer period of time. However, treatment should not be continued for more than four weeks without patient re-evaluation.
Dermol (Viatris) Very potent	Section 4.2 Clobetasol propionate belongs to the most potent class of topical corticosteroids (Group IV) and prolonged use may result in serious undesirable effects (see section 4.4). If treatment

	with a local corticosteroid is clinically justified beyond 4 weeks, a less potent corticosteroid preparation should be considered. Repeated but short courses of clobetasol propionate may be used to control exacerbations (see details below). If the condition worsens or does not improve within 2-4 weeks, treatment and diagnosis should be re-evaluated. Treatment should not be continued for more than 4 weeks. If continuous treatment is necessary, a less potent preparation should be used. The maximum weekly dose should not exceed 50gms/week. Therapy with clobetasol should be gradually discontinued once control is achieved and an emollient continued as maintenance therapy.
Beta (Viatris) Potent	Section 4.2 Apply thinly and gently rub in using only enough to cover the entire affected area once or twice daily for up to 4 weeks until improvement occurs, then reduce the frequency of the application or change the treatment to a less potent preparation.
Diprosone (Viatris) Potent	Section 4.2 In most cases, 4 weeks continuous treatment should be considered the maximum.
Elocon (Organon) Potent	Section 4.2 Babies and children up to four years should not be treated with topical steroids for longer than three weeks. *Comment: there is no warning for adults and children 4 years and over. Note the Australian Elocon product information states that Elocon is indicated for short-term use (up to 4 continuous weeks).*
Advantan (Leo) Potent	Section 4.2 In general, the duration of use should not exceed 12 weeks in adults and 4 weeks in children.
Locoid (Link Pharmaceuticals) Potent	Section 4.4 Babies and children up to four years should not be treated longer than 3 weeks *Comments: No maximum duration for adults and children over 4 years.*
Eumovate (GSK) Moderate	Section 4.2 Apply a thin film and gently rub in, using only enough to cover the affected area twice daily for up to 7 days. If the condition does not improve within the first 7 days or becomes worse, the patient should see a doctor. If after 7 days of treatment, improvement is seen but further treatment is required, the patient should see a doctor.
Aristocort (Pharmacy Retailing t/a HCL) Moderate	Section 4.4 Paediatic use: Long term therapy in infants should be avoided as adrenal suppression may occur. *Comments: No maximum duration for adults.*
DermAid (Douglas) Weak	Section 4.4 Long-term continuous topical therapy should be avoided where possible, particularly in children, as adrenal suppression can occur (even without occlusion). In atopic dermatitis (eczema), a rebound of pre-existing dermatoses can occur with abrupt discontinuation of topical corticosteroid preparations. Therapy with topical corticosteroids should be gradually discontinued once control is achieved and an emollient continued as maintenance therapy.
DP Lotion-HC (Douglas) Weak	Section 4.2 In atopic dermatitis (eczema), a rebound of pre-existing dermatoses can occur with abrupt discontinuation of topical corticosteroid preparations. Therapy with topical corticosteroids

	should be gradually discontinued once control is achieved and an emollient continued as maintenance therapy.
Hydrocortisone 1% cream Ethics (Multichem) Weak	Section 4.4 Long-term continuous topical therapy should be avoided where possible, particularly in children, as adrenal suppression can occur (even without occlusion). Use of the product near the eyes should be avoided.
Hydrocortisone 1% cream (AFT) Weak	Section 4.4 Patients are advised to contact their physician if the condition under treatment worsens or if symptoms persist for more than seven days or if symptoms clear and occur again within a few days.
Hydrocortisone 1% cream (Noumed) Weak	Section 4.4 Patients are advised to contact their physician if the condition under treatment worsens or if symptoms persist for more than seven days or if symptoms clear and occur again within a few days.
Topiderm 1% cream (AFT) Weak	Section 4.4 Long-term continuous topical therapy should be avoided where possible, particularly in children, as adrenal suppression can occur (even without occlusion).

Of note, the Elocon, Locoid and Aristocort data sheets have information on a maximum duration of use in paediatrics but not in adults (see comments in red in Table 11). In the interest of appropriate use of TCS and to minimise potential adverse effects, the MARC could advise Medsafe to request these sponsors to include a maximum duration of continuous use in adults.

The MARC could also advise that all TCS data sheets (or certain potencies) should have a standard warning to regularly review patients using TCS and if possible, to reduce the frequency of application or change to a less potent preparation if the maximum recommended duration of use is exceeded.

Of note, mildly potent steroids (ie, hydrocortisone and clobetasone) must have the advisory warning statement "not to use for more than 7 days, except on the advice of a doctor" on the package labelling, as required by the Label Statements Database (see below).

4.2 Updates to the Label Statements Database

The MHRA will be requiring the package labelling of TCS to state their potency. This could be similarly done in New Zealand through updates to the Label Statements Database.

The Label Statements Database list mandatory warnings and advisory statements that are required on medicines labels under the regulations 13(1)(i) of the Medicines Regulations 1984.

Table 12 outlines the current Label Statements Database requirements for TCS. The warning/advisory statements are only applicable to hydrocortisone, clobetasone and aclometasone (these are TCS available without a prescription) to encourage appropriate use at the consumer level.

Table 12: Label Statements Database entry for topical corticosteroid, 6 December 2024

Substance/Group/Class	Conditions	Statements or requirements	Required by
Corticosteroids, topical Examples include: Alclometasone Clobetasone Hydrocortisone*	For dermal use (alclometasone and clobetasone)	• Do not use for acne. • Do not use on the face. • Do not use under bandages or dressings except on doctor's advice. • Do not use for more than 7 days at a time, except on doctor's advice. • Caution: Contains [names of any preservatives or allergens].	1/8/2011
	For dermal use (hydrocortisone)	• Do not use in children under 2 years old except on doctor's advice. • Do not use for acne. • Keep out of eyes • Do not use under bandages or dressings except on doctor's advice. • Do not use for more than 7 days at a time, except on doctor's advice.	1/8/2011

Source: Medsafe Label Statements Database. Available: https://www.medsafe.govt.nz/regulatory/labelling.asp#form 6 December 2024.

There are several benefits to stating the steroid potency on the package labelling including greater patient awareness and aiding patient in selecting the correct TCS when they are prescribed multiple topical medicines at different potencies. This avoids confusion and reduces the risk of inappropriate use.

However, consideration should be given to the usefulness of stating the potency (mild, moderate, potent and very potent) as the terms may not be meaningful from the patient's perspective. The MHRA has instead used the terms 'mild steroid', 'moderate steroid', 'strong steroid', and 'very strong steroid'. In addition, the pharmacy label can obstruct the statement and many topical products containing TCS are compounded with other ingredients without the original packaging given to the patient.

The MARC could advise that Medsafe undertake a Label Statements Database consultation to have the potency of the steroid stated on the package labelling. Other considerations include whether the potency should also be stated for TCS combination products (ie, TCS combined with an antifungal/ antibiotic/ antiviral/ calcipotriol).

A proposed Label Statements Database entry for consultation is outlined in Table 13. The proposed entry is for all plain TCS regardless of the classification (ie, will include pharmacy only, restricted and prescription TCS).

Table 13: Proposed additional Label Statements Database entry for plain topical corticosteroids

Substance/Group/Class	Conditions	Statements or requirements
Corticosteroids, topical plain	For dermal use For all plain topical corticosteroid regardless of classification	• [insert potency] steroid

4.3 Communication

Guidelines and education materials on appropriate use and application of TCS are available in New Zealand. However, the MARC could advise if further education on TSW, covering what is known about this condition so far, and the reported distinct features, is needed. The article could include information on steroid potencies and general advice on how to minimise the risk of TSW, as outlined in Health Canada's communication [22]:

- Prescribe the lowest potency needed.
- Advise patients on the amount and frequency of application.
- Inform patients on the duration of use, particularly on sensitive areas (eg, face and genitals).

- Switch to a lower potency TCS if treatment is beyond the recommended duration of the time is necessary.
- Taper use or advise periodic breaks in treatment in patients on long-term, continuous TCS treatment.
- Inform patients to seek medical advice if their skin conditions worsen while using TCS or within 2 weeks after stopping treatment.

Medsafe could also highlight the following information from DermNet [11]:

- Reduce the frequency and potency of topical corticosteroid use as soon as inflammatory skin disorders clear (avoid ongoing daily use 'to prevent recurrence').
- Avoid continued use of moderate to potent topical corticosteroids on the face.
- Minimise continuous prolonged corticosteroid treatment duration (eg, over 2 weeks). Some conditions such as vulval lichen sclerosus may need more than 4 weeks therapy to maximise beneficial response.
- Reduce topical steroid potency and application from daily to twice weekly after 2–4 weeks of use.

5 DISCUSSION AND CONCLUSIONS

Significant interest in TSW reactions from consumers in recent years has driven international regulatory review. Published literature mainly consist of systematic reviews and case series, however the quality of evidence at the current time is low. TSW reactions is not a well-defined diagnosis although there appears to be some distinct symptoms that is different from reappearance of the person's original skin disease. Treatment of TSW is unclear.

There appears to be apparent differences of opinion between consumers and healthcare professionals on the existence of TSW reactions, highlighting the need to for further research on TSW.

Despite these challenges, the MHRA has undertaken a review of TSW reactions and are working with sponsors to include TSW as a warning and adverse effect in the TCS product information. The package labelling will also be updated to state the potency of the steroid in the interest of consumer awareness and education when multiple steroid products of different potencies are prescribed.

Other regulators such as the Health Sciences Authority and Health Canada have issued communication on TSW reactions. These communications have generally outlined what is known about TSW reactions so far and that further research is required to better understand TSW reactions. Medsafe is not aware of other regulators taking similar actions to the MHRA.

In 2013, Medsafe published a *Prescriber Update* article highlighting a case of steroid rebound reaction and in 2021 Medsafe requested all TCS sponsors to include rebound effect to the data sheet. This was widely adopted by most sponsors, although some disagreed with this update as their product is only indicated for short-term use. The term rebound effect does not fully capture what is currently known about TSW reactions so updating the data sheet further may be beneficial.

In New Zealand, 16 suspected cases of TSW reactions have been reported. Two-thirds of those were reported in 2021 or after, coinciding with MHRA's review. [redacted]

The MARC is asked to consider the risk of TSW from TCS, and whether regulatory action is required to manage the risk. Regulatory actions may include requesting sponsors to update their data sheets, undertaking a Label Statements Database consultation to include the steroid potency on the package labelling, communication or other appropriate measures.

6 ADVICE SOUGHT

The Committee is asked to advise:

- On the risk of topical steroid withdrawal reactions and if regulatory action is required to manage the risk?
- If other communication is required, other than in MARC's remarks?

7 ANNEXES

Annex 1 – Hajar et al (2015). A systematic review of topical corticosteroid withdrawal ("steroid addiction") in patients with atopic dermatitis and other dermatoses. *J Am Acad Dermatol*

Annex 2 – Hwang J and Lio PA (2022). Topical corticosteroid withdrawal ('steroid addiction'): an update of a systematic review. *J Dermatolog Treat*

Annex 3 – Brookes TS et al (2023). Topical steroid withdrawal: an emerging clinical problem. *Clin Exp Dermatol*

Annex 4 – Barlow R et al (2024). Topical steroid withdrawal: a survey of UK dermatologists' attitudes. *Clin Exp Dermatol*

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