## 1.1. Topical corticosteroids and steroid withdrawal syndrome in atopic eczema

### Introduction

Topical corticosteroids have anti-inflammatory, antipruritic and vasoconstrictive actions. They suppress the inflammatory response and symptoms of different, often with itching associated, conditions.
Topical Corticosteroids (TCS) are divided into four classes, with increasing potency: class 1 weakly potent, class 2 moderately potent, class 3 strongly potent and class 4 very potent (Table 1).

Class 1 corticosteroids can be used in mild forms of dermatitis, including *seborrheic dermatitis* and *eczema*. Class 2 corticosteroids are particularly indicated for the treatment of eczema such as *contact dermatitis, atopic dermatitis, eczema with lichenification, nummular eczema, eczema dyshidroticum,* but also and *psoriasis*.
Class 3 or 4 corticosteroids are indicated for *eczema associated with lichenification, psoriasis, lichen planus, lichen sclerosus, discoid lupus erythematosus, mycosis fungoides, granuloma annulare, palmoplantar pustulosis and chronic lichen simplex* [1] .
If a patient responds inadequately to a TCS class, a higher class TCS can be prescribed. On the other hand, a lower class TCS is suitable as maintenance treatment of dermatoses which have been initially successfully treated with stronger active agents.
Moderate eczema is often constitutional and chronic in nature. The treatment can be classified into an acute phase (1-2 weeks) and a maintenance phase (if necessary, 1-2 months). In the acute phase, the steroid is applied two times per day, while in the maintenance phase it is applied intermittently (several days per week). This prevents a rapid decrease in response (*tachyphylaxis*) as well as the tendency to prescribe an increasingly stronger corticosteroid [1].

Table 1. Classes of topical corticosteroids

| Class 1 | Class 2 | Class 3 | Class 4 |
|---|---|---|---|
| hydrocortisone acetate 1% | clobetasone 0,05%<br>flumetasone 0,02%<br>hydrocortisone butyrate 0,1%<br>triamcinolone acetonide 0,1% | betamethasone 0,05%<br>desoximetasone 0,25%<br>fluticasone (cream 0,05%, ointment 0,005%)<br>mometasone 0,1%17 | Betamethasonedipropionate 0,05% in propyleneglycol<br>clobetasol 0.05 % |

The main local side effects of TCS include atrophy of epidermis and dermis, telangiectasia and striae. Besides, a facial papulopustular perioral and / or periocular dermatitis may develop, which flares after withdrawal of the corticosteroid and is somewhat suppressed by renewed application. This inadvertently leads to the tendency to use the corticosteroid more often [1].
With long-term treatment of chronic dermatoses a steroid dependency may develop, especially with the higher steroid classes, expressing itself in rebound symptoms or flare of the disease after discontinuation of therapy. Therefore, the therapy should be tapered [2]. A rebound effect is described in the SmPCs of several, but not all topical corticosteroids. Lareb received reports of severe skin problems after discontinuation of long term use of topical steroids.

### Reports

Lareb received 19 reports of (steroid) withdrawal syndrome associated with the use of topical steroids, in a period from July 18, 1996 till April 4, 2016. The reports are listed in Table 2.
All patients (one unknown) had (atopic) eczema. The duration of TCS use was many years in most patients, but varied between 3 months and 27 years. Several patients had used various TCS during years, in most cases class 2, 3 or 4 TCS. In several cases the time to onset of the reaction after withdrawal is not known, in others symptoms were reported to have developed within 3-14 days after discontinuation. The symptoms resembled an aggravation of eczema, resulting in renewed lubrication of the skin with the same TCS or even a stronger TCS. In a number of reports it is mentioned that the TCS had been tapered. When the patients abstained from application of TCS the symptoms expanded over the body, even in places where the TCS had not been applied. Several pictures showed a

redness of the skin, with a sharp cutoff between red and normal appearing skin. In the end, after a period of several months, only three patients had not recovered. More details regarding the description of symptoms of the individual reports can be found in appendix 1.

Table 2. Reports of steroid withdrawal syndrome associated with the use of topical steroids

| Patient, Number, Sex, Age, Source | Drug, daily dose Indication for use | Concomitant medication | Suspected adverse drug reaction | Duration of treatment, time after withdrawal, outcome |
|---|---|---|---|---|
| A, 206006<br>F, 21-30<br>consumer | clobetasol 0.5 mg/g<br>eczema | | steroid withdrawal syndrome | 20 years<br>4 days<br>recovering |
| B, 206003<br>F, 41-50<br>physician | clobetasone 0.5 mg/g<br>eczema | salmeterol/fluticasone | steroid withdrawal syndrome, insomnia, alopecia, feeling cold | 20 years<br>days<br>recovering |
| C, 207825<br>F, 21-30<br>consumer | mometasone 1mg/g<br>eczema | | steroid withdrawal syndrome | 14 years<br>3 days<br>recovering |
| D, 211008<br>F, 31-40<br>consumer | clobetasol 0.5 mg/g<br>eczema | ethinylestradiol/ levenorgestrel | steroid withdrawal syndrome, condition aggravation | 16 years<br>10 days<br>recovering |
| E, 211075<br>F, 41-50<br>consumer | triamcinolone,<br>atopic eczema | | steroid withdrawal syndrome | 15 years<br>unknown<br>not recovered |
| F, 199951<br>F, 11-20<br>consumer | clobetasol 0.05 mg/g, fluticasone 0.05 mg/g, hydrocortisone 10 mg/g,<br>eczema | clemastin<br>cromoglicic acid<br>hydroxyzine | dependence, steroid withdrawal syndrome, skin red, pruritus, eye disorder, fatigue, hypersensitivity, depressed mood, general physical health deterioration | years<br>2 weeks,<br>recovered with sequel |
| G, 200800,<br>F, 51-60<br>consumer | hydrocortisone butyrate 1mg/g<br>eczema | | drug withdrawal syndrome, eczema aggravated | 20 years<br>unknown<br>not recovered |
| H, 212995<br>F, 21-30<br>consumer | betamethasone 1 mg/g<br>eczema | cetirizin | face edema<br>steroid withdrawal syndrome | 9 months<br>days<br>recovered/recovering |
| I, 200804<br>F, 21-30<br>consumer | fluticasone 0.05 mg/g<br>atopic eczema | triamcinolone tablet<br>prednisone | drug withdrawal syndrome, pruritus, hyperhidrosis, fatigue, allergy aggravated, depressed mood | 7 years<br>unknown<br>recovering |
| J, 212074<br>F, 21-30<br>consumer | clobetasone 0.5 mg/g, hydrocortisone10 mg/g, triamcinolone 0.1 %, mometasone fluticasone 0.5 mg/g betamethasone 1mg/g<br>eczema | | skin atrophy, eczema aggravated, steroid withdrawal syndrome | 20 years<br>unknown<br>recovering |
| K, 212021 | triamcinolone 0.1 % | | steroid withdrawal | 2 years |

| | | | | |
|---|---|---|---|---|
| M, 21-30<br>consumer | fusidic acid | | syndrome | unknown<br>recovering |
| L, 212256<br>F, 31-40<br>consumer | mometasone 1mg/g,<br>eczema | | steroid withdrawal syndrome | 5 years<br>3 days<br>recovering |
| M, 213366<br>F,31-40<br>consumer | mometasone 1 mg/g<br>hydrocortisone<br>tacroliumus 0.3 mg/g<br>eczema | | steroid withdrawal syndrome | 2-3 years<br>weeks<br>recovering |
| N,213368<br>F, 21-30<br>consumer | mometasone 1mg/g<br>eczema | | steroid withdrawal syndrome | 7 months<br>unknown<br>recovering |
| O,213375<br>F, 31-40<br>consumer | betamethasone<br>clobetasol 0.5 mg/g<br>atopic eczema | ciclesonide | steroid withdrawal syndrome<br>eczema facial | 3 months/1 month<br>unknown<br>recovering |
| P, 214251<br>F, 21-30<br>consumer | clobetasone 0.5mg/g<br>clobetasol 0.5 mg/g<br>eczema<br><br>clobetasol 0.5 mg/g<br>atopic eczema | | steroid withdrawal syndrome | 4 years/3 years<br>soon<br>recovered with sequel |
| Q,200803<br>F, 21-30<br>consumer | | | drug withdrawal syndrome, eczema aggravated, pruritus, sleep disturbance, depressed mood, hyperventilation, panic attacks, (food) allergy aggravated<br><br>withdrawal syndrome | 27 years<br>days<br>recovering |
| R, 75849<br>M, 61-70<br>pharmacist | mometasone 1 mg/g<br>unknown<br><br>betamethasone 1 mg/g<br>eczema | propranolol<br>captopril<br>hydrochlorothiazide | withdrawal syndrome<br>eczema aggravated | 2 years<br>unknown<br>recovering |
| S, 213356<br>F, 11-20<br>consumer | | formoterol/budesonide inhaler | | 9 months<br>unknown<br>not recovered |

## Other sources of information

*SmPC*

Information upon rebound symptoms is described in most SmPCs of topical steroids, except for several SmPCs of hydrocortisone acetate (Fagron, Tiofarma and Cremicort®, class 1) and for clobetasone (Emovate®, class 2). However, in a few SmPCs (hydrocortisone- Calmurid®, fluticasone-Cutivate® / Cortifil® / Fluticrem®, clobetasol-Clobaderm®) rebound symptoms are only described for the indication psoriasis, but not for other dermatoses, including eczema. In most SmPCs no further description upon the rebound symptoms is given. Only for mometasone, dermatitis with intense erythema, burning and paresthesia is mentioned and for Clarelux® (clobetasol) blushing, paresthesia and burning feeling of the skin is described after discontinuation.

The development of rebound symptoms might result in a renewed application of TCS and therefore lead to dependency. In most SmPCs, where rebound symptoms are mentioned, also dependency is described. Only for Betnelan® (betamethasone valerate, class 3) and fluticasone (Cutivate®, Cortifil®, Fluticrem®) no specific information concerning dependency is given.
Information upon tapering of topical corticosteroids is not given for hydrocortisone acetate (class 1), hydrocortisone butyrate (class 2), nor for Diprosone® (betamethasone dipropionate, class 3) [3].
For detailed information, see appendix 2.

*Literature*
A systematic review of 34 studies in association with TCS withdrawal was performed [4]. The majority of patients were women who had used mid- or high potency TCS on their face and genitals for atopic dermatitis. TCS withdrawal was reported mostly on the face and genital area, days to weeks after discontinuation. Burning and stinging were the most frequently reported symptoms (65.5%) with erythema being the most common sign (92.3%). TCS withdrawal syndrome can be divided into two subtypes: 1) erythemato-edematous subtype, with burning and edema. A sharp cut-off between red and normal appearing skin is frequently observed. Also scaling/peeling and papules can be present with itching. Supported care was given by administration of antihistamines and ice/cool compresses. 2) papulopustular subtype, especially when TCS were used on the face. Histology displays findings common to rosacea.
The authors mention some differences between these TCS withdrawal symptoms and a flare-up of the underlying atopic dermatitis: burning as a prominent symptom, confluent erythema within days to weeks after TCS discontinuation and a history of prolonged TCS use.

Topical Steroid addiction (TSA) or inappropriate use (overdosing in class, frequency or period of use) can result in more severe or diverse skin manifestations after the withdrawal from TCS than at pre-application [5]. It is also called Red Burning Skin Syndrome (RBSS). Several stages might appear. In the acute phase, the starting location is a site of intractable prurigo like eruption, where erythema develops after TCS withdrawal. The erythema spread gradually day by day to areas of the skin where TCS have never been applied. A typical spreading course is from face to neck, upper extremities, trunk and then to the lower extremities (but not on hand palm and foot soles; it stops at the margin of the dorsal and palmar or solar sides). Milder cases only show erythema, but this could be accompanied by exudative edema, papules, pustules, erosion an high fever. The peak might be days, but also months after withdrawal. After the acute phase, a dry, itchy, thickened and desquamative skin is observed. The skin is sensitive to various stimuli, like plasters, climate etc. Excessive sweating or itchy wheals sometimes develop. Gradually the skin returns to the original condition (of atopic skin) within weeks to years. Longer periods of application and more potent strengths of the TCS seems to lead to more frequent addiction. Histologically atrophy of the skin from TCS might become obvious as soon as 2- 6 weeks after start of therapy. Probably the symptoms seem to be caused by direct action of TCS to the skin (barrier destruction due to epiderm atrophy). Remedy is complete withdrawal of the TCS.

Rapaport published 2 articles in association with topical steroid addiction. The first one describes 100 cases of red face syndrome after long term use of TCS for chronic eyelid dermatitis [6]. In the second publication [7] he describes similar syndromes in other body areas after administration of increasing potency of TCS for years. These include red scrotum syndrome, vulvodynia, anal atrophoderma, chronic actinic dermatitis and chronic eczema. In the latter case, it involved 56 patients, who had flares with localized vesiculation and oozing, coupled with edema of ankles and hands. Surprisingly, patches of nummular eczema sometimes appeared in distant areas, where there previously had been no involvement. Rapaport describes a pattern of initial flare and a subsequent repeating flares, occurring several weeks later, with each time shorter and less vigorous period of flares and longer period of quiescence.

*Databases*

Table 2. Reports of steroid withdrawal symptoms with topical steroids in the databases of the Netherlands Pharmacovigilance Centre Lareb and the Uppsala Monitoring Centre, WHO Collaborating centre for international drug monitoring [8]

| Database | Preferred Terms | Number of reports |
|---|---|---|
| Lareb | steroid withdrawal syndrome | 14 |
| | drug withdrawal syndrome | 3 |
| | withdrawal syndrome | 2 |
| WHO* | steroid withdrawal syndrome | 90 |
| | drug withdrawal syndrome | 127 |
| | withdrawal syndrome | 131 |

*Details of the reaction are not available, therefore is not sure if this concerns a skin reaction or other reaction

It is not possible to extract data concerning topical corticosteroids from the Eudravigilance database, because searches cannot be performed on ATC codes (i.e. D07A), but only on active ingredients without further specification on pharmaceutical form.

*Prescription data*

*Table 3. Number of patients using topical steroids in the Netherlands between 2010 and 2014 [9]*

| Drug | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| D07AB02 Hydrocortisone acetate | 475,120 | 471,050 | 459,980 | 450,310 | 448,220 |
| D07AB01 Clobetasone (Emovate ®) | 52,011 | 51,393 | 48,156 | 49,606 | 51,988 |
| D07AB02 Hydrocortisone butyrate (Locoid ®) | 141,020 | 137,250 | 134,450 | 131,790 | 132,290 |
| D07AB03 Flumetasone (Locacorten ®) | 1,241 | 1,059 | 1,003 | 841 | 753 |
| D07AB09 Triamcinolone | 573,490 | 568,570 | 570,200 | 556,170 | 553,640 |
| D07AC01 Betamethasone (Diprosone ®) | 260,780 | 258,730 | 251,250 | 251,070 | 267,420 |
| D07AC03 Desoximetasone (Topicorte ®) | 76,585 | 77,030 | 78,594 | 77,982 | 77,229 |
| D07AC06 Diflucortolone (Nerisona ®) | 3,001 | 2,806 | 2,440 | 2,126 | 1,967 |
| D07AC13 Mometasone (Elocon ®) | 128,390 | 130,330 | 130,220 | 131,830 | 141,290 |
| D07AC17 Fluticasone | 116,510 | 115,900 | 114,530 | 113,730 | 111,150 |

| Drug | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| (Cutivate ®) | | | | | |
| D07AD01 Clobetasol (Dermovate ®) | 205,940 | 212,940 | 218,920 | 227,380 | 237,730 |
| Total | 1,974,430 | 1,966,490 | 1,949,820 | 1,932,270 | 1,957,560 |

*Mechanism*

Possible mechanisms might involve an effect on the "skin immune system," a direct effect on blood vessels in the skin or effects on the pituitary adrenal axis. The continuous use of topical or systemic corticosteroids initiates a pre-atrophic phase leading to an atrophic state with tachyphylaxis. With the ensuing atrophy, a burning sensation becomes prominent; continued steroid usage brings on vasoconstriction and soothes the burning. The cycle of repeated vasoconstriction/vasodilation, sometimes called the "neon sign" or "trampoline effect," continues until the vasculature becomes fully dilated as a physiologic response. The mechanism by which this occurs is thought to reflect the suppressive effect of corticosteroids on nitric oxide (NO) in the endothelium. Release of accumulated endothelial NO stores eventuates in "hyperdilation" of vessels beyond their original diameters. Finally, local steroid spread causes extension of erythema, atrophy, and rash beyond the original site and even at distant sites [7].
Recently (immune)histological investigation was performed in eight patients with atopic dermatitis, including one child with short use of TCS, and adult with long history of TCS application and adults with TCS withdrawal and rebound phenomenon [10]. Patchy defects in cortisol production in the epidermis were observed as well as parakeratosis and immature corneal layer formation. The author concluded that prolonged application of TCS might suppress the cortisol production of keratinocytes, which is poorly developed at early ages and completed naturally as to growth. Rebound phenomenon after TCS withdrawal can occur due to the relative insufficiency of cortisol in the epidermis and the immature corneal layer formation.

**Discussion and conclusion**

Lareb has received 19 reports of steroid withdrawal syndrome in association with long term use of class 2-4 topical steroids. In most patients a long-lasting severely burning red skin was present, as a rebound effect after discontinuation of TCS. The association was supported by several publications, which also describe a burning red skin, frequently with a sharp cutoff between red and normal appearing skin.

It is of importance to acknowledge the possible role of (too) long term use of topical steroids followed by abrupt tapering, resulting in a rebound effect. The symptoms might look like a red burning skin syndrome or mimic the initial indication, i.e. (worsening of) eczema. As the difference between original atopic dermatitis and steroid withdrawal symptoms is little in skin manifestation, the conception of TSA has not been widely recognized, even among some dermatologists [10]. As a consequence, it is likely that topical steroids will be re-administered and/or higher doses (or a more potent class) will be applied, resulting in a vicious circle of continued use of topical steroids. This process might be prevented by a strategy of gradual tapering of the topical steroid, e.g. from a potent corticosteroid to a less potent topical steroid.
Instructions on tapering are included in directives for dermatologists and general practitioners [11,12]. In the dermatology directive 'Atopic Eczema' the following instruction is found:
*"In case of long-term use of TCS, in particular Class 3 and 4, of more than 10 g/day, it is important to reduce the used amount slowly. This is necessary to prevent exacerbations of eczema but also to stimulate the adrenal cortex in case of suppressed cortisol production. If this prolonged use involves large skin areas, it is advised to determine cortisol levels. If these are decreased as a sign of resorption, an endocrinologist should be consulted for initiation of a cortisol stress schedule"* [11]. In general, measurement of cortisol levels after intensive TCS treatment is not necessary. However if patients fail to switch to a less potent TCS class due to a rebound effect or fail to taper the amount to less than 50 gram of clobetasol a week, the determination of serum cortisol levels might be considered [13].

The directive ‘Eczema’ for general practitioners contains profound guidance upon the class, dose and duration of use of TCS in atopic eczema. Also a schedule of tapering during a 7 week period is provided [12] .
The directives for dermatologists and general practitioners therefore lack conformity in the treatment schedule of TCS. Beside this, the description of steroid withdrawal syndrome in these documents is minimal. Neither is information hereupon present in a uniform way in the SmPCs of TCS. In order to provide adequate care in the application of topical corticosteroids in eczema detailed information of the corticosteroid withdrawal syndrome and strategy of gradual tapering should be present in the SmPCs of all topical steroids.

- In the SmPCs of all topical corticosteroids, detailed information upon rebound signs and symptoms should be available as well as information upon the risk of dependency. Instructions concerning dose and duration of treatment and gradual tapering should be harmonized.

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**Appendix 1**

**Details of the reactions in association with withdrawal of topical steroids**

Note: patient B is a physican

A, 206006
A female aged 21-30 years, with steroid withdrawal syndrome (red skin syndrome/ steroid addiction syndrome) following administration of clobetasol for eczema with a latency of 20 years after start. She had eczema over her whole body. She used the cream sometimes for a long period and sometimes shortly. Directly after the withdrawn of clobetasol she experienced a fierce reaction with redness, wetting, pruritus and flakes. She was not able to live a normal life for 6 months and was absent from school for months. The medication was reduced, but still these reactions occurred. The patient went to a dermatologist, which did not acknowledge this phenomenon according to the patient. Now, the patient is recovering for at least 10 months. The past drug therapy indicates that the patient had a clobetasol cream (Dermovate®) and experienced the same complaints as well.

B, 2006003
A female physician, aged 41-50 years, with steroid withdrawal syndrome (red skin syndrome/steroid rosacea), insomnia, feeling cold and alopecia following administration of clobetasone for eczema with a latency of 20 years after start and days after discontinuation. The patient used different types of topical steroids during the last 20 years, but used most of the time clobetasone. The patient recovered with sequel from alopecia and is recovering from the steroid withdrawal syndrome, insomnia and cold feeling 2.5 months after the withdrawal. She reduced the dose and use of clobetasone gradually during the withdrawal period and claims that the red facial skin is no exacerbation of here eczema. The red skin is located on face, neck and dorsal side of her wrists/hands (where she never had eczema). Surprisingly her skin at her upper arms, legs, chest and belly is better than it has been in the past 20 years. The medical history indicates that during corticosteroid treatment she suffered several times from a fungal infection (groins, feet and vaginal), herpes infections (with two times a herpes keratitis), and has sun sensitivity for four years. After withdrawal no fungal infection nor a herpes zoster infection occurred. Blood cortisol values are not measured.

C, 207825
No further information

D, 211008
A female aged 31-40 years, with steroid withdrawal syndrome following administration clobetasol for eczema with a latency of 10 days after withdrawal of clobetasol, which had been used for 16 years. The skin condition aggravated to a full body reaction in the following months. The patient is still recovering 1,5 year after the discontinuation. She treated this reaction with an own unspecified product and UVB light therapy.
The patients past drug therapy indicates that the patient experienced aggravated eczema during previous discontinuations of the clobetasol ointment. Since then the patient is also more sensitive for perfume and taking a shower.

E,211075
A female aged 41-50 years, with steroid withdrawal syndrome following administration of triamcinolone for atopic eczema with a latency of 15 years after start and unknown latency after discontinuation. The triamcinolone was tapered before discontinuation. The triamcinolone was not totally withdrawn, but the patient only used the cream if she had eczematous spots. The base of the eczema is located on the hands and sometimes slightly on her face and décolleté. After the withdrawal the eczema aggravates and expand to her neck, arms, abdomen, bikini area and knees. According to the patient, she realized later that this was "red skin syndrome". The complaints started directly after reducing the use of the cream and includes burning and painful skin and extreme pruritus. The dermatologist advised the use of mometasone. In the beginning this helped , but currently she experiences the same complaints during the reduction of mometasone use. The patient has not recovered. The past drug therapy indicates that the patient had betamethasone on an unspecified moment and experienced the same problems after discontinuation.

F, 199951
A female aged 11-20 years, with dependence, steroid withdrawal syndrome, pruritus, eye disorder (without application in the eye, painful and swollen), food allergy aggravated, chronic fatigue, reduced resistance to infections, aggravation of pre-existing lung problems and depressed mood (with death wish) following administration of clobetasol, fluticasone, hydrocortisone for eczema with an unknown latency after start and 2 weeks after the withdrawal of these topical corticosteroids. Further the withdrawal syndrome contains sleeping problems, thin dry skin, blurry vision and gastro-intestinal discomfort. The drugs clobetasol, fluticasone and hydrocortisone were withdrawn several times during a 7 year period of use, resulting in the mentioned reactions, described as ‘red skin syndrome’. Concomitant medications were clemastine, cromoglicic acid, hydroxyzine. The reactions were treated with anti-histaminics, diet and halotherapy. Currently the patient is recovering and recovered with sequel from these adverse drug reactions, having not used any topical steroid anymore for 10 months. She experiences sometimes a flare up, but overall the complaints are less severe. The past drug therapy indicates that the patient had a hydrocortisone/salicylic acid before and experienced these same reactions.

G, 200800
A female aged 51-60 years, with eczema aggravated and drug withdrawal syndrome following administration of hydrocortisone butyrate with a latency of 20 years after start, and unknown latency after withdrawal. The eczema used to be only on the patients hands, but now it is present all over her body. She had severe itching, resulting in sleepless nights. The patient has not recovered. The patient has no known medical history. The patient had the same reaction before after an earlier withdrawal of hydrocortisone.

H, 212995
A female aged 21-30 years, with steroid withdrawal syndrome (described as 'red skin syndrome') and face edema following withdrawal of betamethasone for eczema. The past drug therapy indicates that the patient had hydrocortisone cream used daily

on her face and triamcinolone acetonide cream for 3 weeks prior to the betamethasone. The eczema spread to the arms, face, neck and belly. The patient recovered from the face edema after 6 weeks, The 'red skin syndrome' worsened the first 2 months, but improved after 4 months. According to the patient the dermatologist does not acknowledge this withdrawal syndrome.

I 200804
A female aged 21-30 years, with pruritus, hyperhidrosis, fatigue, allergy aggravated and depressed mood, drug withdrawal syndrome and eczema aggravated following administration of fluticasone for atopic eczema with a latency of 7 years after start and unknown latency after withdrawal. Especially the first 6 months after discontinuation, she suffered from very severe eczema. She visited the Emergency Room for several hours because of eczema herpetic, which was treated with acyclovir. The past drug therapy indicates that the patient had topical hydrocortisone before for 13 years, but had to switch to stronger corticosteroids, even oral therapy, because it had no effect anymore. After withdrawal, the patient was treated with antihistaminics. The patient is recovering (3 years after withdrawal). Concomitant medications were triamcinolone, prednisone.

J, 212074
A female aged 21-30 years, with skin atrophy, eczema aggravated and steroid withdrawal syndrome (described as red skin syndrome) following administration of triamcinolone, clobetasone, hydrocortisone, fluticasone, mometasone, tacrolimus, betamethasone for eczema with an unknown latency after the withdrawal of different topical corticosteroids. She usually used the topical corticosteroids a few days, alternately with a few days with no use; total usage around 20 years, gradually from less potent to very potent drugs. Because of skin atrophy she decides to stop with all creams and ointments. She experienced an extreme aggravation of her eczema and the described red skin syndrome for which she was hospitalized for 3 weeks. She was treated with tar ointment and later on with sea salt, acupuncture,special unspecified diets. It took 2 years for her skin to improve.

K, 212021
A male aged 21-30 years, with steroid withdrawal syndrome (described as red skin syndrome) following administration of triamcinolone/fusidic acid for atopic eczema with a latency of 2 years after start. The reporter mentioned that, due to misinformation and ignorance, he used the triamcinolone cream for too long. After an initial successful treatment, the symptoms returned. After 6 months the patient experienced red spots besides the normal symptoms for eczema. The use of the cream remedied these symptoms and red spots. However more and more spots arose over the whole body. The skin was very thin and breaks easily. Eyes and nipples were also inflamed. In addition, the patient mentioned that his immune system had long been disturbed which caused itching and much sweating and unexplained nerve pain. The patient mentioned further that research showed that the only solution to get the problems resolved was the so called ‘cold-turkey quit’. Withdrawal symptoms are dry red skin, massive itching, insomnia, neuralgia, swollen eyes, anxiety, mood swings, extreme burning (skin was on fire). The patient is recovering for 2.5 months now. Some parts of the skin have healed and the withdrawal symptoms are diminishing.

L, 212256
A female aged 31-40 years, with steroid withdrawal syndrome following administration of mometasone for eczema with a latency of 5 years after start and 3 days after withdrawal of mometasone. Red skin syndrome (not further specified) occurred when the patient did not use the ointment at least once a week. The dose for mometasone was increased. The patient is recovering. The patient mentioned that stress and weather conditions worsen the symptoms.

M, 213366
A female aged 31-40 years, with steroid withdrawal syndrome following administration of mometasone, tacrolimus, hydrocortisone for eczema with a latency of several years after start of the topical corticosteroids and weeks after the withdrawal The complaints were described as aggravation of the eczema. After the withdrawal she experienced a red and warm skin / pruritus / wet spots, also at places where she had not used the corticosteroids or had eczema. The whole upper body was affected. The drug mometasone, tacrolimus and hydrocortisone were withdrawn. The patient is recovering a year later, but still experiences redness and pruritus at her hands.

N, 213368
A female aged 21-30 years, with steroid withdrawal syndrome following administration of mometasone for eczema with a latency of 7 months after start. The drug mometasone was withdrawn. The patient is recovering. The past drug indicates that the patient had an unspecified class I topical corticosteroid on an unspecified moment.

O, 213375
A female aged 31-40 years, with eczema facial (perioral dermatitis) and steroid withdrawal syndrome following administration of betamethasone and clobetasol for atopic eczema with a latency of 3 months, respectively 1 month after start. The drugs clobetasol and betamethasone were withdrawn. The perioral dermatitis was treated with fusidic acid cream . The patient is recovering.

P, 214251
A female aged 21-30 years, with steroid withdrawal syndrome following administration of clobetasol and clobetasone for eczema with a latency of respectively 3 an 4 years after start and soon after the withdrawn of these topical corticosteroids. The patient mentioned that she lubricated respectively 10 and 20% of her body with the topical corticosteroid clobetasol and clobetasone. The drug clobetasol and clobetasone were withdrawn. The first five months, she experienced a burning skin, generalised redness, pruritus and wet spots. Then, some recovery started. The patient recovered with sequel 18 months after the withdrawal; some lichenification of the skin remained.

Q 200803
No more details

R, 75849
A male aged 61-70 years, with withdrawal syndrome (red spots in his face) when stopping mometasone cream after 2 years of use. First he used it as needed. Later on he needed it more and more frequently, because a reaction developed, when trying to stop mometasone. Patient was treated with minocycline, topical metronidazole/hydrocortisone acetate and is recovering.

S, 213356

A female aged 11-20 years, with eczema aggravated and withdrawal syndrome following administration of betamethasone topical for eczema with a latency of 9 months after start. In first instance, the dose for betamethasone was increased. After discontinuation the symptoms got worse. The reporter mentioned the complaints could also be due to the weather (winter) and stress. Patient was treated with homeopathy. The patient has not recovered.

**Appendix 2**
**SmPCs topical corticosteroids: Information upon rebound, dependence or tapering**

| Class | Composition | Brand name or manufacturer name | Marketing Authorization Number (RVG) | Rebound | Dependence | Tapering | Remarks |
|---|---|---|---|---|---|---|---|
| 1 | hydrocortisone acetate | Fagron | 20729 | - | - | - | |
| | | Fagron | 25186 | - | - | - | |
| | | Tiofarma | 33923 | - | - | - | |
| | | PCH | 51010 | R[1] | D[1] | - | |
| | | Cremicort® | 10997 | - | - | - | |
| | | Calmurid, HC crème® | 06996 | RP[2] | - | - | with urea |
| | | | | | | | |
| 2 | hydrocortisone butyrate | Locoid crelo® | 16163 | R[1] | D[1] | - | |
| | | Locoid crème® | 05911 | R[1] | D[1] | - | |
| | | Locoid oleogel | 05909 | R[1] | D[1] | - | |
| | | Locoid scalp lotion® | 05910 | R[1] | D[1] | - | |
| | | Locoid vet crème® | 09344 | R[1] | D[1] | | |
| | | | | | | | |
| 2 | clobetasone | Emovate® | 07519 | - | - | T [3,4] | |
| | | Emovate® | 07520 | - | - | T [3,4] | |
| | | | | | | | |
| 2 | flumetasone | Locacorten® | 04475 | R | D | T [5] | |
| | | Locasalen® | 05901 | R [6] | D [6] | T [3,4,5] | with salicylic acid |
| | | | | | | | |
| 2 | triamcinolone | Apothecon | 33659 | R[1] | D[1] | T[7] | |
| | | Fagron | 20730 | R[1] | D[1] | T[7] | |
| | | Teva | 51531 | R[1] | D[1] | T[7] | |
| | | DMB | 33941 | R[1] | D[1] | T[7] | |
| | | Basic Pharma | 51893 | R[1] | D[1] | T[7] | |
| | | CF | 50801 | R [6] | D [6] | T[7] | |
| | | Basic Pharma | 56785 | R[1] | D[1] | T[7] | |
| | | Basic Pharma | 52672 | R [6] | D [6] | T[7] | |
| | | PCH | 50060 | R [6] | D [6] | T[7] | |
| | | | | | | | |
| 3 | betamethason valerate | PCH | 16002 | R [6] | D [6] | T[8] | |
| | | PCH | 16003 | R [6] | D [6] | T[8] | |
| | | PCH | 16004 | R [6] | D [6] | T[8] | |
| | | Betnelan crème® | 04519 | R [9,10] | - | T [3,4,9,10,11] | |
| | | Betnelan zalf® | 04520 | R [9,10] | - | T [3,4,9,10,11] | |
| | | Betnelan vloeistof® | 05650 | R [9,10] | - | T [3,4,9,10,11] | |
| | | Betnelan emulsie® | 17806 | R [9,10] | - | T [3,4,9,10,11] | |
| 3 | betamethasone diproprionate | Diprosone crème® | 06650 | R [6] | D [6] | - | |
| | | Diprosone lotion® | 08211 | R [6] | D [6] | - | |
| | | Diprisone zalf® | 06864 | R [6] | D [6] | - | |
| | | Diprosalic zalf | 09375 | R [6] | D [6] | T [13] | with salicylic acid |
| | | | | | | | |
| 3 | mometasone furoate | Elocon® | 14173 | R [1,12] | D [1] | T [12] | |
| | | Elocon® | 14174 | R [1,12] | D [1] | T [12] | |
| | | Elocon® | 14332 | R [1,12] | D [1] | T [12] | |
| | | Auden | 115296 | R [1,12] | D [1] | T [12] | |
| | | Auden | 115297 | R [1,12] | D [1] | T [12] | |
| | | Glenmark | 100972 | R [1,12] | D [1] | T [12] | |
| | | Mylan | 100967 | R [1,12] | D [1] | T [12] | |
| | | Ovixan | 115559 | R [1,12] | D [1] | T [12] | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Monovo | 105118 | R [1,12] | D [1] | T [12] | |
| | | Monovo | 104067 | R [1,12] | D [1] | T [12] | |
| | | Sandoz | 115250 | R [1,12] | D [1] | T [12] | |
| | | | | | | | |
| 3 | desoximethasone | Topicorte® | 05829 | R [6, 14] | D [6,14] | T [15] | |
| | | Ibaril ® | 08164 | R [6] | D [6] | T [16] | |
| | | | | | | | |
| 3 | fluticasone | Cutivate crème® | 16647 | RP[2] | - | T [3, 4, 11, 17] | |
| | | Cutivate zalf® | 16648 | RP[2] | - | T [3, 4, 11, 17] | |
| | | Cortifil® | 102106 | RP[2] | - | T [18] | |
| | | Fluticrem® | 102091 | RP[2] | - | T [18] | |
| | | | | | | | |
| | | | | | | | |
| 4 | betamethasone diproprionate in propylene glycol | Diprolene zalf® | 09522 | R [6] | D [6] | T [19] | |
| | | Diprolene hydrogel® | 11173 | R [6] | D [6] | T [19] | |
| | | | | | | | |
| 4 | clobetasol | Dermovate zalf® | 06933 | RP [2,20] | - | T [3, 4, 11 20, 21] | |
| | | Dermovate creme® | 06932 | RP [2,20] | - | T [3, 4, 11 20, 21, 22] | |
| | | Dermovate lotion® | 07579 | RP [2,20] | - | T [3,4,11, 20, 22] | |
| | | Clarelux® | 30096 | R [23] | D [23] | T [23] | |
| | | Clobaderm creme® | 114753 | RP [2] | - | T [24] | |
| | | Clobaderm zalf® | 114754 | RP [2] | - | T [24] | |
| | | Clobex shampoo® | 33440 | R [25] | D [25] | T[25] | |

R: information upon rebound
RP: information upon rebound, when used in psoriasis
D: information upon dependence
T: information upon tapering

Text (inDutch):
1 “Rebound-effect", wat kan leiden tot afhankelijkheid van steroïden
2 Gebruik bij psoriasis kan leiden tot generalisering, excessieve systemische absorptie en reboundrecidieven bij het staken van het gebruik
3 Bij verminderde lever/nierfunctie :Vanwege het toegenomen risico op atrofie en op remming van de adrenale cortex door systemische absorptie, met name bij langdurige behandeling en behandeling van grotere oppervlakken van de huid, wordt aanbevolen de behandeling geleidelijker af te bouwen dan bij patiënten zonder verminderde lever-/nierfunctie om symptomen van hypercorticisme te voorkomen.
4 Bij ouderen: Vanwege het toegenomen risico op atrofie en op remming van de adrenale cortex door systemische absorptie, met name bij langdurige behandeling en behandeling van grotere oppervlakken van de huid, wordt aanbevolen de behandeling geleidelijker af te bouwen dan bij jongere volwassenen om symptomen van hypercorticisme te voorkomen.
5 De behandeling van chronische huidaandoeningen (bv psoriasis) dient niet plotseling gestaakt te worden
6 Na langdurige behandeling voor chronische dermatosen, kunnen rebound-verschijnselen optreden. Dit kan tot steroïdafhankelijkheid leiden
7 Na verbetering is twee- tot driemaal per week aanbrengen meestal voldoende. Per week niet meer dan 30-60 gram crème aanbrengen.
8 Na verbetering kan het aantal applicaties teruggebracht worden tot eenmaal per dag of minder.
9 Behandeling met Betnelan moet geleidelijk worden afgebouwd zodra de behandelde aandoening onder controle is. Bij het plotseling stoppen met het gebruik van betamethason kunnen bestaande dermatosen heroptreden.
10 Dit kan worden herhaald totdat verbetering optreedt; daarna kan het aantal toepassingen worden verlaagd tot enkele malen per week of kan de
behandeling worden voortgezet met een minder sterk preparaat of, bij droge schilferige aandoeningen, een emolliens.
11 In geval van een overdosering moet de toediening geleidelijk worden afgebouwd door het verminderen van het aantal toepassingen, of door het gebruik van een minder sterk corticosteroïd, vanwege het risico op glucocorticosteroïdinsufficiëntie.
12 Zoals met alle potente lokale glucocorticoïden moet het plotseling staken van de behandeling vermeden worden. Wanneer de langdurige lokale behandeling met potente glucocorticoïden wordt gestopt, kan rebound optreden in de vorm van dermatitis met intense roodheid, tintelingen
en branderigheid. Dit kan worden voorkomen door de behandeling langzaam af te bouwen door bijvoorbeeld over te gaan op een intermitterende basis alvorens de behandeling volledig te stoppen.
13 Nadat de aandoening met Diprosalic is onderdrukt moet dit zo mogelijk worden vervangen door een product met een lager werkingsniveau
14 Na langdurige behandeling met matig sterke, sterke en zeer sterke corticosteroïden kunnen na stoppen reboundverschijnselen optreden. Dit kan leiden tot steroïd afhankelijkheid.
15 Afhankelijk van de aard van de aandoening kan 1 tot 4 maal per dag een kleine hoeveelheid emulsie op de huid worden aangebracht. Na verbetering van de symptomen kan worden volstaan met een eenmaal daagse applicatie
16 in de meeste gevallen dient de crème aanvankelijk drie maal daags dun op de te behandelen huidgedeelten aangebracht te worden en zo mogelijk licht te worden ingemasseerd. Later is eenmaal per dag aanbrengen meestal voldoende.
17 Behandeling met Cutivate moet geleidelijk worden afgebouwd zodra de behandelde aandoening onder controle is. Bij het plotseling stoppen met het gebruik van fluticasonpropionaat kunnen bestaande dermatosen heroptreden. Breng een- of

tweemaal daags een dun laagje aan dat genoeg is om de gehele aangedane huid te bedekken en wrijf dit voorzichtig op de aangedane huid. Dit kan worden herhaald totdat verbetering optreedt; daarna kan het aantal toepassingen worden verlaagd tot enkele malen per week of kan de behandeling worden voortgezet met een minder sterk preparaat of, bij droge schilferige aandoeningen, een emolliens.
18 Duur van het gebruik: De dagelijkse behandeling dient te worden voortgezet totdat de aandoening goed onder controle is. Daarna dient de applicatiefrequentie tot de laagst werkzame dosis te worden verlaagd. Wanneer CORTIFIL voor de behandeling van kinderen wordt gebruikt, moet met de
behandeling worden gestopt indien binnen 7-14 dagen geen verbetering is opgetreden; het kind moet dan opnieuw worden beoordeeld. Zodra de aandoening onder controle is (doorgaans binnen 7-14 dagen), dient de applicatiefrequentie te worden verlaagd tot de laagst werkzame dosis gedurende de kortst mogelijke tijd. Continue dagelijkse behandeling gedurende meer dan 4 weken wordt niet aanbevolen. Verhoging van het aantal dagelijkse applicaties kan bijwerkingen verergeren zonder dat de therapeutische effecten verbeteren.
19 Zoals met alle sterk werkzame, lokaal toe te passen corticosteroïden het geval is, dient de behandeling met Diprolene zalf te worden gestaakt als de huidaandoening verbeterd is, en indien nodig worden vervangen door een product van een lager werkingsniveau.
De duur van de behandeling met Diprolene zalf varieert van enkele dagen tot een langere periode, afhankelijk van het klinische beeld, maar mag de duur van vier opeenvolgende weken niet overschrijden zonder controle van de aandoening. In het algemeen mag niet meer dan 30-60 mg zalf
per week worden gebruikt
20 Behandeling met Dermovate moet geleidelijk worden afgebouwd zodra de behandelde aandoening onder controle is. Bij het plotseling stoppen met het gebruik van clobetasol kunnen bestaande dermatosen heroptreden.
21 Breng een- of tweemaal daags een dun laagje aan dat genoeg is om de gehele aangedane huid te bedekken en wrijf dit voorzichtig op de aangedane huid. Behandeling moet niet langer dan 4 weken worden gecontinueerd zonder dat de huidconditie van de patiënt wordt gecontroleerd. Na verbetering
kan het aantal applicaties worden teruggebracht tot eenmaal per dag of minder of kan de behandeling worden voortgezet met een minder sterk preparaat of, bij droge, schilferige aandoeningen, een emolliens
22 Een geringe hoeveelheid ’s morgens en ’s avonds aangebracht op de hoofdhuid totdat verbetering is vastgesteld, is meestal voldoende. Daarna kan het aantal toepassingen worden teruggebracht tot eenmaal per dag of minder.
23 Wanneer de behandeling na langdurig gebruik plotseling wordt stopgezet, kan een rebound-effect worden waargenomen in de vorm van blozen en een prikkelend en branderig gevoel van de huid. Dit kan worden vermeden door de behandeling geleidelijk aan af te bouwen.
Topische corticosteroïden kunnen gevaarlijk zijn omdat rebound-relapsen kunnen volgen op de ontwikkeling van tolerantie.
24 Een- of tweemaal per dag een dun laagje aanbrengen op de aangetaste huid, tot er verbetering is. Zoals bij andere sterk werkende, plaatselijke steroïden moet de behandeling beëindigd worden als de aandoening onder controle is. In de beter reagerende aandoeningen kan dit al binnen een paar dagen gebeuren. Als binnen twee tot vier weken geen verbetering te zien is, moet misschien de diagnose herzien of doorverwezen worden. Korte kuren met Clobaderm mogen herhaaldelijk gebruikt worden om exacerbaties onder controle te krijgen. Als continue behandeling met steroïden noodzakelijk is, dan moet een minder sterk middel gebruikt worden.
Langdurige en intensieve behandeling met sterk werkzame corticosteroïden kan verwijding van de oppervlakkige bloedvaten veroorzaken, met name bij huidplooien of als occlusief verband gebruikt wordt.
25 Lokale corticosteroïden moeten met voorzichtigheid worden gebruikt om verschillende redenen, zoals het optreden van rebound relapses na het beëindigen van de therapie, het ontwikkelen van tolerantie (tachyfylaxie), en het ontwikkelen van lokale of systemische toxiciteit. De duur van de behandeling moet worden beperkt tot maximaal 4 weken. Zodra klinische resultaten worden waargenomen moet de shampoo met grotere tussenpozen worden aangebracht, of moet deze indien nodig worden vervangen door een alternatieve behandeling. Als er binnen vier weken geen
verbetering optreedt kan het nodig zijn om de diagnose te heroverwegen. Herhaalde kuren met Clobex 500 microgram/g shampoo kunnen worden toegepast om verslechtering te beheersen mits de patiënt onder regelmatige medische controle staat.