Review paper

Alclometasone dipropionate: properties and clinical uses

Katarzyna Kisiel[1,2], **Andrzej Kaszuba**[1]

[1]Department of Dermatology, Paediatric Dermatology and Oncological Dermatology, Medical University of Lodz, Poland
Head: Prof. Andrzej Kaszuba MD, PhD
[2]Department of Paediatric Dermatology, Specialized Hospital, Warsaw, Poland
Head: Lidia Ruszkowska MD

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Abstract

Topical glucocorticosteroids are the mainstay of therapy in inflammatory skin disorders. The therapeutic effect of glucocorticosteroids depend on their chemical structure, physio-chemical properties, concentration of the active substance, pharmaceutical form, and affinity for specific receptors.

Alclometasone dipropionate is a new-generation non-fluorinated topical glucocorticosteroid used in the treatment of inflammatory glucocorticosteroid responsive skin disorders (i.e. atopic dermatitis, contact dermatitis, psoriasis vulgaris, lichen planus) in adults and in pediatric patients older than 1 year of age. The unique properties of the compound result from the presence of a chlorine atom in position 7α which increases the potency of its effect without increasing the incidence of local and systemic adverse effects.

Apart from its characteristic properties of glucocorticosteroids as a class (it is anti-inflammatory, antiproliferative, immunosuppressant and vasoconstrictive) the preparation has a beneficial effect on skin hydration which makes alclometasone the glucocorticosteroid of choice in dermatoses associated with pruritus and excessive skin dryness. Adverse reactions to alclometasone are rare and usually mild and transient. Alclometasone dipropionate is available in two formulations, i.e. 0.05% cream and 0.05% ointment.

Key words: alclometasone dipropionate, glucocorticosteroids, inflammatory skin disorders, pruritus, adverse reactions.

Introduction

Topical glucocorticoids are the mainstay of therapy in inflammatory skin disorders. Due to a broad spectrum of activity (anti-inflammatory, antiproliferative, immunosuppressant and vasoconstrictive) they are used in the treatment of numerous dermatoses in adults and children. Hydrocortisone was the first topical glucocorticoid introduced in therapy in 1952. In the following years, further research was conducted to improve the effect of topical glucocorticoids by increasing their anti-inflammatory and immunosuppressant activity with a concomitant decrease in their potential for adverse effects. An ideal topical glucocorticoid should penetrate across the stratum corneum of the epidermis and attain appropriate concentrations in the skin but little of it should reach the systemic circulation (i.e. it should have a good anti-inflammatory effect with minimal untoward systemic effects). This may be achieved by increasing the lipophilicity of topical steroids, by e.g. their esterification. The newest topical glucocorticoids, including alclometasone dipropionate, demonstrate greater anti-inflammatory activity and lower atrophogenic potential, and rarely cause hypersensitivity cross- reactions [1, 2].

Classification

The therapeutic effect of glucocorticoids depends on their chemical structure, physico-chemical properties, concentration of the active substance, pharmaceutical form (the vehicle [base]) and affinity for specific receptors. According to these criteria, glucocorticoids have been subdivided into several classes [3].

According to the European classification, topical glucocorticoids are subdivided into four groups by the potency of their therapeutic effect. Group I includes the least potent agents and group IV the most potent ones. Accord-

Address for corespondence: Katarzyna Kisiel MD, Department of Paediatric Dermatology, Specialized Hospital, Bursztynowa 2, 04-749 Warsaw, Poland, tel. +48 22 47 35 212, e-mail: kkilian@wp.pl

ing to the American classification, topical glucocorticoids are subdivided in seven groups with group I including the most potent agents and group VII the least potent ones. The two classifications of topical glucocorticoids (American and European) are presented in Tabs. 1-2, respectively.

Mechanism of action

Topical glucocorticoids, first introduced in dermatology over 50 years ago, are widely used in the treatment of skin disorders. However, despite a long history of their therapeutic use, the precise mechanism by which glucocorticoids exert their effects remains largely unknown. At the cellular level, alclometasone, like other glucocorticoids, after crossing the cell membrane binds to specific glucocorticoid receptors (GCR) in the cytoplasm [5]. Subsequently, the glucocorticoid-GCR complex moves into the nucleus, where its binds to DNA at specific regions, known as the glucocorticoid response elements (GRE). At further stages, the expression of certain genes is either

Tab. 1. American topical corticosteroids classification according to potency (by the National Psoriasis Foundation modified)

Group	International name	Concentration [%]	Formulation
I Very potent	Clobetasol propionate	0.05	Ointment, cream, lotion
	Betamethasone propionate	0.05	Ointment, gel
II Potent	Betamethasone dipropionate	0.05	Cream
	Halcinonide	0.1	Ointment, cream
	Mometasone furoate	0.1	Ointment
	Desoximetasone	0.25	Ointment, cream
	Desoximetasone	0.05	Gel
III Potent	Amcinonide	0.1	Cream, lotion
	Fluocinonide	0.05	Cream
	Fluticasone propionate	0.005	Ointment
	Triamcinolone acetonide	0.1	Ointment
	Betamethasone valerate	0.1	Ointment
	Desoximetasone	0.05	Cream
IV Moderately potent	Mometasone furoate	0.1	Cream
	Triamcinolone acetonide	0.1	Ointment, cream, aerosol
	Fluocinolone acetonide	0.025	Ointment
	Hydrocortisone valerate	0.2	Ointment
V Moderately potent	Fluticasone propionate	0.05	Cream
	Betamethasone valerate	0.1	Ointment, cream
	Betamethasone dipropionate	0.05	Lotion
	Desonide	0.05	Ointment
	Triamcinolone acetonide	0.1	Lotion
	Fluocinolone acetonide	0.025	Cream
	Hydrocortisone butyrate	0.1	Cream
	Hydrocortisone valerate	0.1	Ointment
VI Moderately potent	Fluocinolone acetonide	0.01	Cream, lotion
	Alclometasone dipropionate	0.05	Ointment, cream
	Desonide	0.05	Cream
	Betamethasone valerate	0.1	Lotion
VII Less potent	Products containing hydrocortisone, dexamethasone, flumetasone, methylprednisolone and prednisolone		

stimulated (transactivation) or inhibited (transuppression) [5].

In clinical practice, glucocorticoids are used for their anti-inflammatory, immunosuppressant and antiproliferative effects [3, 6]. The anti-inflammatory effect is due to the reduction in production, release and activity of mediators of inflammation (kinins, histamine, lysosomal enzymes, prostaglandins and leukotrienes) and proinflammatory cytokines, including IL-1, Il-3, IL-4, IL-5, IL-6, IL-8, TNF-α and GM-CSF [7-9]. By triggering constriction of blood vessels and decreasing their permeability glucocorticoids additionally restrict the influx of inflammatory cells to the lesion. Due to their immunosuppressant properties (inhibiting of proliferation of T- and B-lymphocytes, Langerhans cells and mastocytes), glucocorticoids reduce the severity of both immediate and delayed hypersensitivity reactions (types I and IV) [10] while their antiproliferative effect (resulting from the inhibition of DNA and collagen synthesis) inhibits tissue hyperplasia, characteristic of e.g. psoriasis [11, 12].

Pharmacology

Alclometasone dipropionate (Fig. 1) is a new-generation, non-fluorinated topical glucocorticoid, used in the treatment of inflammatory glucocorticoid-responsive skin disorders. It demonstrates anti-inflammatory, immunosuppressant and vasoconstrictive activity [2, 13, 14].

The alclometasone dipropionate [7α-chloro-11β,17,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dione 17,21-dipropionate) molecule is obtained by insertion of a chlorine atom in position 7α of 16α-methylprensoline 17,21-dipropionate. The unique properties of the compound result from the presence of a chlorine atom in position 7α instead of positions C6 or C9, which increases the potency of its effect without increasing the incidence of local and systemic adverse effects. Additionally, as a highly lipophilic compound, alclometasone dipropionate rapidly penetrates into the skin where its active metabolites bind to specific receptors [2, 14, 15].

The potency of alclometasone – assessed in clinical trials comparing the efficacy of different topical glucocorticoids in the treatment of inflammatory dermatoses – is equal to the potency of clobetasone butyrate, desonide and hydrocortisone butyrate. Alclometasone is more effective or of comparable efficacy to 1% hydrocortisone (cream or ointment), but less potent than betamethasone dipropionate ointment [14, 16].

Alclometasone dipropionate is available in two formulations, i.e. 0.05% cream and 0.05% ointment. It is a white powder, insoluble in water, slightly soluble in propylene glycol and moderately soluble in hexylene glycol. Each gram of the medicinal product contains 0.5 mg of alclometasone dipropionate in a hydrophilic emollient base with propylene glycol as one of the ingredients (cream) or in an ointment base of hexylene glycol (ointment). In addition to these two substances, the vehicles (bases) contain other ingredients responsible for the physico-chemical properties of the products (ease of application, absorption, maintaining the right concentration of the active substance in the skin) [13, 17, 18].

Tab. 2. European topical corticosteroids classification according to potency (by the British National Formulary 2004, modified)

Group	International name	Concentration [%]
I Less potent	Hydrocortisone	0.5 and 1.0
	Hydrocortisone acetate	1.0
	Dexametasone	0.01-0.1
	Methylprednisolone	0.25
	Prednisolone	0.5
	Fluocinolone acetonide	0.0025
	Alclometasone dipropionate	0.05
II Moderately potent	Betamethasone benzoate	0.025
	Betamethasone dipropionate	0.05
	Flumethasone pivalate	0.02
	Betamethasone valerate	0.025
	Clobetasone butyrate	0.05
	Triamcinolone acetonide	0.02
	Fluocinolone acetonide	0.05
III Potent	Fluocinolone acetonide	0.1
	17-hydrocortisone butyrate	0.1
	Diflucortolone valerate	0.1
	Betamethasone valerate	0.1
	Betamethasone dipropionate	0.05
IV Very potent	Clobetasol propionate	0.05
	Halcinonide	0.1

The extent of percutaneous penetration and absorption of alclometasone is determined by the pharmaceutical form (cream or ointment) and the vehicle (base), but also by the local skin condition (thickness and integrity of the epidermis, local inflammatory processes, skin damage), character and location of the skin lesions and the use of occlusive dressings. Approximately 3% of alclometasone is absorbed (during 8 h of application on intact skin), it is metabolised in the liver and its metabolites are eliminated via the kidneys [2, 13, 14].

Duchkova *et al.* [19] have found that in addition to the effects typical of glucocorticoids alclometasone improves skin hydration (Fig. 2). The observed increase in skin hydration may indirectly relieve pruritus, which is often caused by excessive skin dryness (especially in children and the

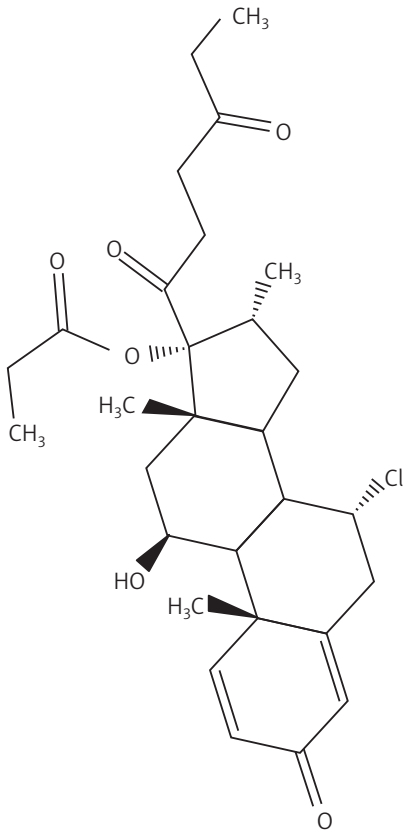

Fig. 1. Scheme of alclometasone dipropionate

elderly). For that reason, alclometasone may replace alternating use of glucocorticoids and emollients [19].

It must be emphasised that animal studies did not reveal any toxic effects of alclometasone administered intraperitoneally and orally at doses approximately 3000-fold higher than the recommended human doses. Also, there have been no published reports from *in vivo* and *in vitro* studies of any carcinogenic and mutagenic effects of alclometasone [14].

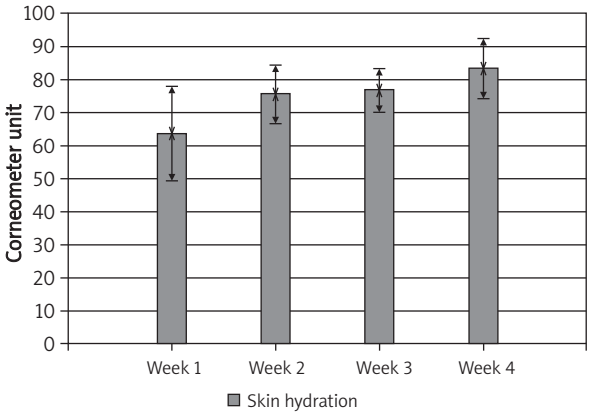

Fig. 2. Increase in skin hydration during 4-weeks treatment with 0.5% alclometasone dipropionate cream

Contraindications

Before initiating treatment with alclometasone it is necessary to consider contraindications to its use and potential adverse effects. The optimal treatment (type and duration) and formulation should be chosen, taking into consideration the kind of disorder, character and location of skin lesions and the patient's age. Contraindications to alclometasone use are listed in Tab. 3 [2, 13, 17].

Use during pregnancy and lactation

There are no randomised clinical studies of topical glucocorticoid use in pregnant women. Some topical glucocorticoids have been shown to be teratogenic in laboratory animals. However, studies of alclometasone in laboratory animals did not reveal any adverse effects (teratogenic, embryotoxic or of any other kind) on the foetus [14, 17]. On the other hand, as with other topical glucocorticoids there are no well-controlled studies in pregnant women or documented case reports of alclometasone use in pregnancy. There are no data concerning crossing of the placental barrier by alclometasone. Alclometasone dipropionate has been classified as the FDA category C of drug safety during pregnancy (irrespective of the trimester of pregnancy), which means that it should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus [13, 14, 17].

Experts' recommendations on the use of alclometasone during breastfeeding are inconsistent. There are no well-controlled studies or documented case reports of use in nursing mothers and the effects on breastfed neonates and infants. Since the risk of untoward side effects in the breastfed babies related to the topical administration of alclometasone in the nursing mother cannot be exclud-

Tab. 3. Contraindications to alclometasone use

- Hypersensitivity to alclometasone dipropionate or any of the other ingredients of the product
- Skin infections (viral, bacterial, fungal or parasitic)
- Post-vaccination skin reaction
- Delayed wound healing
- Acne vulgaris, acne rosacea
- Cutaneous tuberculosis
- Perioral dermatitis
- Diaper dermatitis
- Application into or around the eye
- Use in paediatric patients below 1 year of age

ed, the use in a nursing woman should occur only if the potential benefit justifies the potential risk to the baby. When alclometasone preparation is used, it should be applied to the patient's skin after nursing or a few hours before another feeding. The degree in which topically administered alclometasone is excreted with breast milk has not been determined [13, 14, 18].

Therapeutic indications

Alclometasone dipropionate is indicated for the treatment of corticosteroid-responsive dermatoses with pruritic and local inflammatory manifestations (i.e. atopic dermatitis, contact dermatitis, psoriasis, lichen planus) in adult and paediatric patients of 1 year of age or older [13, 14]. Particular indications for alclometasone use in adults and paediatric patients are described below. Use in the elderly is described in a separate section.

Indications for alclometasone use in adult patients

Atopic dermatitis

Topical glucocorticoids are the mainstay of therapy in atopic dermatitis (AD) and studies confirm the efficacy of alclometasone in the treatment of AD. Duke *et al.* [20] compared alclometasone dipropionate (0.05% ointment) and clobetasone butyrate (0.05% ointment) in the treatment of AD. In 64 adult patients (age 14-74 years) included in the study and randomly assigned to one of the two treatment groups, the study preparation was applied twice daily for 21 days. Both preparations demonstrated comparable efficacy. At the end of the treatment, improvement (reduction in erythema, pruritus and induration) was seen in 75% of the alclometasone-treated patients and 68% of the clobetasone-treated patients. The reported adverse effects were mild: some skin irritation (moderate redness and burning at the site of alclometasone application) and itching and burning in clobetasone-treated patients [20]. In another multicentre, randomised, double-blind study, alclometasone cream 0.05% and hydrocortisone cream 1% were compared in AD patients. In 249 patients (aged 12 or over) included in the study, the randomly selected preparation was applied 3 times a day for 21 days without occlusion. The study was completed by 229 patients (the remaining patients were lost to follow-up). Local improvement of lesions was observed as early as the end of the first week of treatment (at least moderate improvement in 72% of the alclometasone-treated patients and 58% of the hydrocortisone-treated patients). At the end of the treatment, obviously better effects (clearing or considerable improvement of the lesions) were seen in the alclometasone-treated patients compared to the hydrocortisone-treated patients. Tolerability was good. The reported local adverse effects were transient and mild, i.e. local irritation and burning at the site of application [21].

Psoriasis

The efficacy of alclometasone dipropionate cream and ointment in the treatment of psoriasis has been confirmed by numerous studies. In preclinical tests, alclometasone demonstrated anti-inflammatory activity in the treatment of psoriasis, comparable to that of betamethasone valerate and triamcinolone acetonide, but with less frequent untoward effects, local or systemic [22]. In clinical studies, the efficacy of alclometasone in the treatment of psoriasis was comparable to the effects of moderately potent steroids (class II in the European classification and class V in American classification): clobetasone butyrate [23] and desonide [24, 25] and superior to hydrocortisone [26]. On the other hand, betamethasone dipropionate proved more effective than alclometasone.

Frost *et al.* [24] compared in a double-blind, randomised study alclometasone dipropionate ointment 0.05% (ointment) and desonide ointment 0.05% (ointment) in 73 patients with moderate to severe psoriasis. The preparations were applied twice daily without occlusion. Both produced rapid improvement of erythema, induration and scaling. Substantial improvement was evident after 1 week (moderate improvement in 58% of the alclometasone-treated patients and 44% of the desonide-treated patients). At the end of the study the results were similar in both groups with alclometasone being very slightly more effective (differences between the groups were not statistically significant). No adverse drug reactions were observed [24]. A comparison of alclometasone ointment 0.05% and desonide ointment 0.05% in 42 patients with psoriasis yielded similar results. Before the study the preparations were tested by the vasoconstriction assay in healthy volunteers. Although the clinical effects of both preparations were the same, the vasoconstriction assay demonstrated the superiority of alclometasone over desonide [25]. Comparable clinical efficacy and safety of use were observed in patients with psoriasis treated with either alclometasone cream 0.05% or clobetasone cream 0.5% [23]. The study by Cornell *et al.* [25] also compared the efficacy of alclometasone and betamethasone in 42 patients with *psoriasis vulgaris*, who applied the preparations twice daily for 14 days. The study was preceded by the vasoconstriction assay and although the effects on the calibre of blood vessels were similar, the evaluation of clinical efficacy demonstrated obvious superiority of betamethasone dipropionate compared to alclometasone dipropionate [25]. On the other hand, hydrocortisone 1% proved much less effective than alclometasone in the treatment of psoriasis manifestations. In a large randomized study (242 patients, twice-daily applications for 21 days), some lesion improvement (decreased scaling) was observed as early as week 1 and

at the end of the study the superiority of alclometasone over hydrocortisone was obvious and statistically significant with improvement of scaling, erythema and induration. Clinical improvement (moderate to marked) or clearing of the signs and symptoms was observed in 52% of the alclometasone-treated patients compared to 34% of the hydrocortisone-treated patients while symptom aggravation or no treatment effects were reported from 14% the alclometasone-treated patients vs. 27% of the hydrocortisone-treated patients. The frequency and character of adverse reactions were comparable in the two groups (localized pruritus, burning and erythema in 7 alclometasone-treated patients and 6 hydrocortisone-treated patients) [26].

Seborrhoeic dermatitis

Alclometasone administered twice daily for the symptomatic treatment of seborrhoeic dermatitis (SD) in adults demonstrated efficacy comparable to that of hydrocortisone 1%. During a 6-week study no untoward reactions were observed in any of 51 patients treated with alclometasone although the preparation was also applied to sensitive skin areas (face, scalp, behind the ears). On the other hand, evidence of skin atrophy was found in one patient treated with hydrocortisone ointment [27].

Other steroid-responsive dermatoses

Numerous studies cited above emphasize the efficacy of alclometasone in the treatment of psoriasis and atopic dermatitis but equally good treatment effects are also seen in other steroid-responsive inflammatory dermatoses.

In one study, alclometasone cream and ointment 0.05% were used in the treatment of 238 patients (> 12 years of age) with chronic recurrent inflammatory dermatoses (atopic dermatitis, contact dermatitis, lichen planus, lichen simplex chronicus, nummular dermatitis, psoriasis, seborrhoeic dermatitis). The treatment produced a substantial reduction in the severity of signs and symptoms or their clearing in most of the patients (83% of 129 patients applying the cream and 87% of 109 patients applying the ointment). Some improvement could be observed as early as week 1 of the treatment. No adverse drug reactions were reported [28]. Panja *et al.* [29] compared the efficacy of alclometasone ointment 0.05% and hydrocortisone cream 1% in the treatment of chronic recurrent inflammatory dermatoses (atopic dermatitis, contact dermatitis, lichen planus, lichen simplex chronicus, nummular dermatitis). The study was carried out in 101 patients, 14 years of age or older. The preparations were applied twice daily for 21 days. Obvious local improvement was observed in week 2 of the study. At the end of the study, substantial improvement or clearing of the signs and symptoms were reported in both treatment groups although the frequency of full remission was higher in the alclometasone group [29].

The efficacy of alclometasone cream and ointment in the treatment of neurodermatitis (ND) and allergic contact dermatitis (ACD) in adults and children was confirmed by a large multicentre study in 393 patients (246 patients with neurodermatitis and 147 patients with allergic contact dermatitis). Substantial improvement or clearing of the signs and symptoms were observed in both conditions while the treatment outcome was somewhat better in ACD. Both cream and ointment were highly valued (high treatment efficacy, minimal adverse reactions) by both patients and physicians. The preparations were assessed as very good for the symptomatic treatment of neurodermatitis by 64.7% of the physicians and 63.8% of the patients while 72.6% of the physicians and patients assessed it as effective for the treatment of ACD. Adverse drug reactions (pruritus, burning, sensation of tight skin, exacerbation of lesions) were reported in 6 patients (3 patients with ND and 3 patients with ACD) while in 8 patients (5 patients with ND and 3 patients with ACD) the treatment was discontinued as no clinical improvement was achieved [30].

The results of the studies described above are summarized in Tabs. 4-6.

Indications for alclometasone use in paediatric patients

Alclometasone dipropionate is effective in the treatment of skin disorders not only in adults. Numerous studies have also confirmed its efficacy and safety of use in paediatric patients.

Most of the studies evaluated the use in atopic dermatitis. Very good effects were obtained with alclometasone cream and ointment once daily, used for 3 days and during 3 following weeks (a total of 9 applications) in 16 children with AD of different severity. In children with mild to moderate AD (< 20% of the body surface area affected) substantial improvement was observed after 1 week with complete clearing of the symptoms and signs by the end of treatment. In a group of patients with severe AD (> 25% of the body surface affected) the improvement was gradual with the severity reduced by 50% after 3 weeks. At a follow-up visit two weeks after the end of the treatment no evidence of recurrence was observed in any of the treatment groups [2]. Crespi *et al.* [31] obtained similar results in their evaluation of the safety and efficacy of alclometasone dipropionate 0.05% cream applied twice daily for 21 days in the treatment of eczematous lesions in the course of atopic dermatitis, seborrhoeic dermatitis, diaper dermatitis and psoriasis simplex in 39 children aged 3 months to 12 years. After treatment, complete clearing of symptoms and signs was observed in most children and in the remaining 18% – marked or moderate improvement was reported. No local and systemic adverse

Tab. 4. Clinical effectiveness comparison of alclometasone dipropionate and other topical glicocorticosteroids in AD treatment of adults and children

Authors	Treatment	How often applied	Treatment duration [days]	Number of patients	Clearance or improvement after treatment (> 75%)	Lesion reduction [%]
Adults						
Duke (r, sb)	ALC 0.05% ung	BID	21	33	75%	> 75
	CLO 0.05% ung	BID		31	68%	> 75
Bagatell	ALC 0.05% cr	TID	21	114	66%	> 75
	HYD 1.0% cr	TID		115	57%	> 75
Children						
Lassus (r, db)	ALC 0.05% cr	BID	14	22 (age 5-11)	100%	85
	CLO 0.05% cr	BID		21	95%	86
Lassus (r, db)	ALC 0.05% cr	BID	14	20 (age 5-11)	95%	76
	HYDB 0.1% cr	BID		20	80%	70
Mobacken (r, db)	ALC 0.05% ung	BID	21	30 (29) (age 3-16)	93%	> 75
	HYD 1.0% ung	BID		30 (29)	62%	> 75
Kuokkanen	ALC 0.05% ung	BID	21	34 (32) (age 2-10)	88%	> 75
	HYD 1% ung	BID		34 (32)	86%	> 75

cr – cream, ung – ointment, db – double-blind study, sb – single-blind study, r – randomised study, ALC – alclometasone dipropionate, HYD – hydrocortisone, HYDB – hydrocortisone butyrate, CLO – clobetasone butyrate, in brackets (...) – number of patients who completed the study and patients' age

Tab. 5. Clinical effectiveness comparison of alclometasone dipropionate and other topical glicocorticosteroids in the treatment of moderate severe psoriasis vulgaris

Authors	Treatment	How often applied	Treatment duration [days]	Number of patients	Clearance or improvement after treatment (> 75%)
Aggerwal *et al.* (r, sb)	ALC 0.05% cr	BID	21	16	
	CLO 0.5% cr	BID		15	
Cornell *et al.* (r, db)	ALC 0.05% ung	BID	21	42	
	DES 0.05% ung	BID		42	
Frost *et al.* (r, db)	ALC 0.05% ung	BID	21	33	40%
	DES 0.05% ung	BID		33	35%
Kalivas (r, db)	ALC 0.05%	TID	21	117	52%
	HYD 1%	TID		125	34%
Cornell (r, db)	ALC 0.05% ung	BID	14	42	
	BET 0.05% ung	BID		42	

BET – betamethasone dipropionate, DES – desonide, other abbreviations – see Tab. 4

drug reactions were reported and morning plasma cortisol levels prior to, during and after the study remained within the normal range (Fig. 3).

Also Makarova *et al.* in their study (Fig. 4) using alclometasone dipropionate cream 0.05% in 39 children aged 2 to 22 months, with severe to moderate atopic dermatitis found marked improvement (reductions in skin lesion severity by 80.9%, in skin lesion area by 79.8%, in pruritus by 90.3% and in sleep disorders by 83%), no recurrence of the symptoms and signs after treatment and further improvement in the local skin condition after the completion of treatment. The treatment was well tol-

Tab. 6. Clinical effectiveness comparison of alclometasone dipropionate and other topical glicocorticosteroids in the treatment of steroids-sensitive inflammatory dermatoses

Authors	Disease	Treatment	How often applied	Treatment duration [days]	Number of patients	Clearance or improvement after treatment (> 75%)
Panja *et al.*	AD, CD, LSCh, Ecz, LP	ALC 0.05% cr	BID	21	52	90.5%
		CLO 1.0% cr	BID		49	77.8%
Sharma	AD, CD, Ecz, LSCh, Ps, SD, LP, St. d.	ALC 0.05% cr	BID	21	129	83%
		ALC 0.05% ung	BID		109	87%
Lipozencic	ND, ACD	ALC 0.05% cr	BID	21	147 (ACD)	72%
		ALC 0.05% ung	BID		246 (ND)	63.8%

ACD – allergic contact dermatitis, AD – atopic dermatitis, CD – contact dermatitis, Ecz – eczema, LP – lichen planus, PR – prurigo (nodular prurigo), Ps – psoriasis, SD – seborrhoeic dermatitis, ND – neurodermatitis, LSCh – lichen simplex chronicus, St. d. – eczema venostaticum, other abbreviations – see Tab. 4, 5

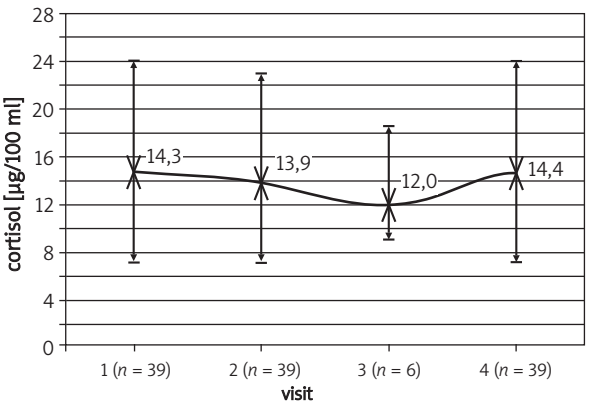

Fig. 3. Mean plasma cortisol levels children treated with alclometasone dipropionate

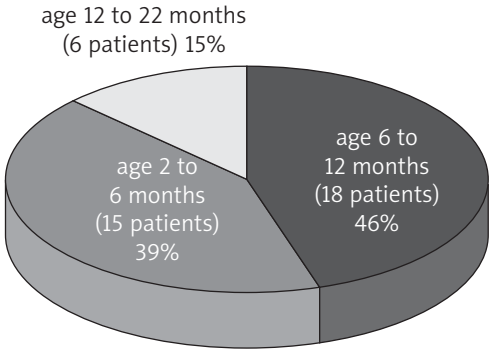

Fig. 4. Distribution of children age

erated and no side effects were observed in the patients, including children below 1 year of age [15].

A number of other studies compared the efficacy and safety of alclometasone and other topical glucocorticosteroids. Lassus, in a randomised, double-blind study, compared the efficacy and safety of alclometasone dipropionate cream 0.05% to clobetasone butyrate cream 0.05% and hydrocortisone butyrate cream 0.1% in the treatment of atopic dermatitis (twice-daily applications for 14 days). In 43 patients (aged 5 to 11 years) alclometasone dipropionate cream 0.05% and clobetasone butyrate cream 0.05% were used and in a separate study in 40 children (aged 5 to 11 years) alclometasone dipropionate cream 0.05% and hydrocortisone butyrate cream 0.1% were administered. Clinical improvement, i.e. improvement in erythema, lesions thickness and pruritus after 7 and 14 days of treatment was observed in all patients. The efficacy of alclometasone and clobetasone was similar (85% vs. 86% of reduction in skin lesions) while hydrocortisone demonstrated a weaker effect than alclometasone (76% vs. 70% of reduction in skin lesions). Transient stinging at the site of application was reported in 4% of the alclometasone-treated patients [32, 33]. Also in a study by Mobacken *et al.* [34] alclometasone proved to be more effective than hydrocortisone. That randomised, double-blind study was performed in 60 patients aged 3 to 16 years treated with either alclometasone ointment 0.05% and hydrocortisone ointment 1%. Improvement of signs and symptoms such as erythema, induration, pruritus, scaling and excoriation was observed after 21 days in all patients, but the outcome was better (statistically significant difference) in the alclometasone-treated group. Kuokkanen and Sillantaka [35] reported different results from their randomised, double-blind study comparing the efficacy of alclometasone ointment 1% vs. hydrocortisone ointment 1% (twice-daily applications for 21 days) for the treatment of eczema in paediatric patients. The mean improvement after treatment (reduced severity of the signs and symptoms or their clearing) was similar in both groups. Tolerability was good in both treatment groups and no evidence of skin atrophy, such as thinning or striae was observed at any of application sites. In one patient only urticaria was reported in week 1 (after usage of both products).

Alclometasone use in geriatric patients (65 years of age and older)

Considering that chronic inflammatory dermatoses are fairly frequent in the elderly, it is important to evaluate the efficacy and especially safety of topical glucocorticoids in this age group. According to Fitzpatrick [36], various inflammatory dermatoses affect 40% of patients aged 65 to 74 years. Skin involution occurring naturally with advancing age, i.e. epidermal thinning, slowing of the process of exfoliation of epidermal cells, decreased epidermal lipid synthesis and skin hydration, degenerative changes in collagen and elastic fibres and atrophic changes in the pilosebaceous apparatus, are conducive to the development of dermatoses with the resulting impairment of the protective and defensive function of the skin. At the same time, skin changes which occur with age affect the efficacy of topical preparations and the safety of their use [36-38].

Moressi *et al.* [39] compared alclometasone dipropionate cream 0.05% and hydrocortisone butyrate cream 0.1% in the treatment of steroid-sensitive dermatoses in patients older than 60 years. Treatment produced obvious improvement in skin lesions in up to 82% of the patients, which was comparable in the two groups, and complete clearing of the signs and symptoms in five patients. The treatment was well tolerated and no adverse effects, including evidence of skin atrophy, were observed. Serum cortisol levels remained within the normal range. Skin biopsy was performed twice (prior to and after treatment) for histomorphometric analysis. Alclometasone demonstrated better penetration into the skin (and tropism) compared to hydrocortisone butyrate and features of skin atrophy were not found.

Zvezdina *et al.* [37] used alclometasone ointment 0.05% and hydrocortisone ointment 1% in elderly patients treated for chronic recurrent eczema. The study was conducted in 44 patients aged 60 to 88 years complaining of chronic, persistent, pruritic eczematous lesions and dryness, burning and sensation of tightness of the skin. The preparations were applied twice daily for 4 weeks with a weekly evaluation of the local skin condition. More rapid local improvement and substantially better outcome at the end of treatment (clinical evaluation using the dermatological index symptom scale) were achieved in the alclometasone-treated patients. Additionally, hydration, surface lipids and pH of the skin were evaluated twice, prior to treatment and after its completion. Prior to treatment in all study patients sebumetry (skin surface lipids) and corneometry (skin hydration) findings were markedly decreased and pH-metry findings were abnormal (alkaline pH in 59.1% of the patients and acidic pH in 36.4%). After alclometasone treatment the study parameters returned to normal. That was not observed after hydrocortisone treatment (skin surface lipids remained at the lower limit of normal, hydration was below normal and pH remained the same). Changes in the study parameters were induced by the base of alclometasone dipropionate ointment applied. Its ingredients (propylene glycol, hexylene glycol, white wax and white petrolatum) provide occlusion and prevent liquid evaporation from the epidermis and increase the rate at which the active substance (alclometasone dipropionate) penetrates into the deeper skin layers. Although the penetration was good and the preparation was well absorbed by the skin, no adverse drug effects, either local or systemic, were reported. In both study groups cortisol levels declined slightly after treatment, but remained within the limits of normal (5-20 µg/dl), which shows that alclometasone may be safely used in the elderly [37].

Dermatoses with severe pruritus are an important therapeutic problem in dermatology, especially in the elderly. It is estimated that in different age groups pruritic dermatoses account for 15% to 40% of all skin disorders and in the elderly the proportion is higher at 48%. The problem becomes more noticeable with the increasing life expectancy and hence increasing proportion of the elderly in the general population [38]. Zvezdina *et al.* [38] compared the effects of alclometasone dipropionate ointment 0.05% and hydrocortisone acetonide ointment 1% on selected skin parameters in patients with eczema and severe skin itching. The study was conducted in 50 patients (39 patients with chronic eczema and 11 patients with senile pruritus) aged 60 to 89 years with the complaints of skin dryness, severe itching and burning. The patients were subdivided into three groups. Group 1 was treated with alclometasone as monotherapy; group 2 received alclometasone, antihistaminics and emollients, while group 3 was given hydrocortisone, antihistaminics and emollients. Alclometasone and hydrocortisone were applied twice daily for 4 weeks. More rapid clinical improvement and substantially higher treatment efficacy were observed in the alclometasone-treated groups. The evaluation included not only the clinical signs and symptoms, but also such parameters such as hydration, surface lipids and pH of the skin. Prior to treatment, markedly decreased sebumetry and corneometry findings as well abnormal pH were observed in the affected skin areas in all patients. In the apparently healthy skin, the findings were at the lower limit of normal. After treatment with alclometasone, hydration and surface lipids of the skin either returned to normal or markedly improved while in the hydrocortisone-treated patients, skin hydration was evidently decreased while surface lipids remained at the lower limit of normal [38]. Duchkova *et al.* [19] also noted that alclometasone in addition to its typical glucocorticosteroid activity has a beneficial effect on skin hydration. The authors evaluated the effect of alclometasone dipropionate treatment on the skin hydration status. The preparation was applied twice daily on the skin of the forearm in 22 healthy adult volunteers. Clinical evaluation and corneometry were performed every 7 days. After 4 weeks

of treatment, skin hydration improved in approximately 21% of the subjects and no adverse effects were reported (Fig. 2).

The authors suggest that improved skin hydration may have a beneficial effect on skin itching, which often results from its dryness and occurs not only in children with AD, but very frequently also in the elderly patients in the course of various inflammatory dermatoses and age-related decrease in skin hydration. Due to this earlier unreported moisturizing property, a topical glucocorticoid preparation may become an alternative to the so-called sandwich method, that is alternate use of glucocorticoids and emollients in the treatment of chronic skin disorders while alclometasone could act as the so-called barrier cream [19].

Results of the studies confirm the efficacy of alclometasone in the treatment of pruritic dermatoses in the elderly and its beneficial effect on the functional status of the skin and its regeneration. It must be emphasized that absence of untoward side effects makes this treatment especially suitable for geriatric patients since with numerous involution changes due to old age, particular caution must be exercised during topical treatment. Taking into consideration the properties of alclometasone described above and safety of its use, no dosage adjustment is recommended in geriatric patients (65 years of age or older).

Dosage

Adults

A thin film of the preparation (cream or ointment) should be applied to the affected skin areas 2-3 times daily and gently massaged. The preparation may be used with occlusive dressings in the treatment of recurrent, chronic dermatoses such as psoriasis or local neurodermatitis (chronic lichen simplex). Like other topical glucocorticoids, the preparation should not be used on the face and around the eyes because of potential adverse effects (inflammation of the skin of the face, perioral dermatitis, skin atrophy, acneiform eruptions, glaucoma and cataract). When alclometasone should be used on the face, the application should be short-term and not under occlusion [13, 17, 18].

Paediatric patients

Dosage and administration are similar in paediatric and adult patients. However, the risk for systemic adverse effects is higher in paediatric patients [13, 14]. The skin of children and infants is more delicate than the adult skin as the epidermis is thinner, stratum corneum, stratum granulosum and stratum spinosum are underdeveloped and there are fewer collagen and elastic fibres in the dermis [40, 41]. Its function of the dermo-epidermal barrier is not fully developed, which facilitates the absorption of topical glucocorticosteroids with the resulting effect on the hypothalamic-pituitary-adrenal (HPA) axis and linear growth retardation. Additionally, a higher ratio of skin surface area to body mass in paediatric patients is associated with a relatively larger skin surface area from which topical steroids are absorbed and hence a higher risk of adverse systemic effects [14, 15, 31]. The risk of adverse effects related to alclometasone use in children is directly proportional to the surface area of the application and increases with application to the areas where glucocorticoid absorption is increased (e.g. face, skin folds, scrotum) and treatment duration. Accordingly, alclometasone should be used in paediatric patients for the shortest possible time (not longer than 3 weeks) and in the smallest effective doses [13, 15, 17]. The preparation is not recommended for use in premature babies, neonates and infants due to a higher risk of increased absorption. The safety of alclometasone use in paediatric patients below 1 year of age has not been established and there are no adequate, randomised studies in large patient groups [13, 17]. However, Makarova and Crespi conducted studies in small groups of patients aged 2 months and older and did not observe any adverse effects, either local or systemic in this age group (Figs. 3-4) [15, 31]. When alclometasone is absolutely indicated in infants, its short-term use is recommended (the smallest effective amount used for a very short period of time). It should not be applied in the diaper area under occlusion (even without occlusion, the absorption from the pudendal area is 42 times greater than from the skin of the arm and the inflammation itself increases percutaneous alclometasone absorption) and between skin folds (they act similarly to occlusive dressings). Parents or guardians should be given precise instructions concerning the preparation use (amount of the preparation, application frequency, treatment duration, need to avoid occlusion, e.g. diapers or plastic pants when the preparation is applied to the diaper area) [13, 17].

Tolerability and adverse effects

Due to potential adverse effects, caution must be exercised when topical glucocorticosteroids, including alclometasone, are administered for the treatment of skin disorders.

Adverse skin reactions

Local adverse reactions to alclometasone are rare. They are usually transient and mild to moderate. The most common adverse effects (reported in approximately 1% to 5.4% patients) include local skin irritation (itching, burning, erythema, stinging) lasting a few minutes to several days [13, 14]. Less common are mild papular rashes, moderate eczema and fungal skin infections [14, 43]. The product information provided by the manufacturer and based

on the reports concerning other topical glucocorticoids includes a warning that the following local adverse reactions may occur in 0.1% to 1% of patients: folliculitis, acneiform eruptions, perioral dermatitis, allergic contact dermatitis, hypopigmentation and skin atrophy, hypertrichosis, miliaria, striae and secondary infection of the treated lesions [18, 19].

No evidence of skin atrophy (including increased number of cases of striae) was observed in clinical studies in adults and children treated with alclometasone for 3 and 6 weeks, even when the preparation was applied to the sensitive areas such as the face, scalp and behind the ears or with occlusive dressings. On the other hand, hydrocortisone administered under occlusion for 24 h did not demonstrate increased transcutaneous penetration, which however markedly increased when occlusive dressings were used for 96 h [17, 18]. That is why, although there have been no reports of skin striae with alclometasone treatment, its use with occlusive dressings is not recommended, especially in children and the elderly because their skin is more delicate and thinner and adverse effects may occur. Local allergic reactions have been reported with alclometasone, i.e. contact dermatitis confirmed by patch tests in a few patients treated with alclometasone [44-46]. Discontinuation of the preparation and symptomatic treatment produced rapid improvement and clearance of the signs and symptoms of allergy. However, it must be remembered that long term topical administration of glucocorticoids may lead to the development of contact allergy to these medications. When hypersensitivity to alclometasone dipropionate has been diagnosed, the medication should be promptly discontinued and treatment with other glucocorticoids of the same structural class avoided as the risk of cross reaction is high [47, 48]. Occasionally, cross-reactivity may occur between different glucocorticoids as it was reported for alclometasone dipropionate (class D1) and budesonide (class B) [49].

Adverse ocular reactions

Application of glucocorticoid preparations into the conjunctival sac may cause an increase in intraocular pressure in approximately 30% of patients [50]. The increase in intraocular pressure occurs a few days to a few weeks after the first application of a glucocorticoid and is usually reversible 1-2 months after withdrawal of treatment. Onset may be sudden with acute glaucoma [51]. There have been no reports of evidence of elevated intraocular pressure, glaucoma and cataract after alclometasone application. However, due to a high risk of these adverse reactions, alclometasone should not be used on the eyelids. When necessary, the application should be short-term and without an occlusive dressing [13, 14, 17].

Systemic adverse reactions

Since preparations containing glucocorticosteroids are absorbed through the skin, alclometasone treatment carries a potential risk of adverse systemic reactions such as the hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing syndrome, low plasma cortisol levels, mild intracranial hypertension, growth retardation in children, hyperglycaemia and glycosuria [13, 14]. Therefore, the preparation should not be applied to a large surface area and damaged skin or to areas under long-term occlusion. In paediatric patients, application of topical glucocorticoids to > 20% of the body surface increases the risk of systemic adverse effects and HPA axis suppression manifested as low plasma cortisol levels and lack of response to the ACTH stimulation [17, 18]. These systemic adverse effects are extremely rare and associated mostly with incorrect use of topical glucocorticoids. Such adverse effects have not been reported with alclometasone, but taking into consideration a potential risk, it is advised to use alclometasone on the high-absorption areas such as under arms, groin areas and skin folds only for a very short time. Particular caution should be exercised during use in patients with liver impairment, paediatric patients and the elderly [13, 14].

Thornfeldt *et al.* [43] assessed the effect of alclometasone on the HPA axis in healthy volunteers. Alclometasone dipropionate (30 g of 0.05% cream) was applied to 80% of the body surface area of normal subjects twice daily for 21 days with daily 12-h periods of total body occlusion. In 10 healthy volunteers it did not affect the HPA axis, which was confirmed by morning plasma cortisol levels, 24-h urinary excretion of 17-hydroxysteroids and urinary free cortisol levels. Although alclometasone was given at much higher doses than recommended, cortisol levels remained within normal limits and there was no evidence of skin atrophy, including striae. Transient local skin reactions such mild papulopustular rash, fungal infection of the lower legs and moderate eczema as well as headache and fatigue were reported by 6 patients. The symptoms did not seem to be related to the topical treatment. They were most likely related to occlusion (wearing of a plastic body suit for 12 h) and the hot, moist climate in which the study was conducted [43]. In another study of alclometasone applied to 30% of the body surface area for 7 days with 12-h or 24-h periods of occlusion, mild reductions (about 10%) in average plasma and urinary free cortisol levels and urinary levels of 17-hydroxysteroids were observed, suggesting slight suppression of the HPA axis. Similar findings were reported from a study in paediatric patients treated with alclometasone twice daily for 3 weeks without occlusion [17]. Therefore, although there have been no reports of systemic complications with alclometasone treatment, if the preparation has to be applied to a large surface area and for longer periods of time (especially in paediatric patients and the elderly) periodical monitoring of A.M. plasma cortisol levels and urinary free cortisol levels as well as the ACTH stimulation are recommended [14, 17].

Summary

Alclometasone dipropionate, a new-generation glucocorticoid for topical use is an effective, well-tolerated preparation with a very good safety profile as confirmed by numerous clinical studies.

It is very effective in the treatment of atopic dermatitis, psoriasis vulgaris, seborrhoeic dermatitis and other steroid-responsive inflammatory dermatoses in paediatric patients and adults.

Apart from its properties characteristic of glucocorticoids as a class (it is anti-inflammatory, antiproliferative, immunosuppressant and vasoconstrictive), the preparation has a beneficial effect on skin hydration. This increase in skin hydration makes alclometasone a glucocorticoid of choice in dermatoses associated with pruritus and excessive skin dryness, which are a common therapeutic problem, especially in the elderly.

Alclometasone dipropionate acts promptly and effectively (the effects of treatment can be observed after a few days), but does not produce any serious adverse effects, either local or systemic, in paediatric patients and adults. It may be safely used in the treatment of inflammatory skin conditions and pruritic dermatoses.

References

1. Brazzini B, Pimpinelli N. New and established topical corticosteroids in dermatology: clinical pharmacology and therapeutic use. Am J Clin Dermatol 2002; 3: 47-58.
2. Capkova S. Afloderm – results of verification study. Dermatovenereological Clinic, Prague.
3. Miller JA, Munro DD. Topical corticosteroids: clinical pharmacology and therapeutic use. Drugs 1980; 19: 119-34.
4. Necela BM, Cidlowski JA. Mechanisms of glucocorticoid receptor action in noninflammatory and inflammatory cells. Am Thorac Soc 2004; 1: 239-46.
5. Schacke H, Schottelius A, Docke WD, et al. Dissociation of transactivation from transrepression by a selective glucocorticoid receptor agonist leads to separation of therapeutic effects from side effects. PNAS 2004; 101: 227-32.
6. Hallam NF. The use and abuse of topical corticosteroids in dermatology. Scott Med J 1980; 25: 287-91.
7. Gilman AG, Rall TW, Nies AS, et al. Goodman and Gilman"s The Pharmacological Basis of Therapeutics. 8th ed. Pergamon Press. Elmsford, NY 1990.
8. Greaves MW, Kingston WP. Topical steroids and the pharmacology of inflammation. In: Mechanisms of topical corticosteroid activity. Wilson L, Marks R (eds). Churchill Livingstone, Edinburgh 1976; 114-20.
9. Weissmann G, Thomas L. Studies on lysosomes. The effects of endotoxin, endotoxin tolerance and cortisone on the release of acid hydrolases from a granular fraction of rabbit liver. J Exp Med 1962; 116: 433-50.
10. Ricciatti D, Lester RS. Topical corticosteroid therapy. Mod Med Can 1977; 67: 546-54.
11. Goodwin P. The effect of corticosteroids on cell turnover in the psoriatic patient. Br J Dermatol 1976; 94 (Suppl): 95-100.
12. Marks R, Williams K. The action of topical corticosteroids on the epidermal cell cycles. In: Mechanisms of topical corticosteroid activity. Wilson L, Marks R (eds). Churchill Livingstone, Edinburgh 1976; 39-46.
13. Afloderm krem – dokumenty rejestracyjne. Ministerstwo Zdrowia, Departament Polityki Lekowej i Farmacji, Warszawa 01.12.2008.
14. Micromedex, Healthcare Series: Document. Drugdex Evaluations: Alclometasone, 05.10.2005:1-9. www.thomsonhe.com/hcs/librarian/PFDefaultActionid/pf.PrintReady.
15. Makarova IV, Gajduk IM, Źiglinskaja OV, et al. Alclometasone dipropionate in the treatment of atopic dermatitis in young children. Quest Mod Ped 2004; 3: 84-6.
16. Kint A. Treatment of atopic dermatitis in children: alclometasone dipropionate cream 0,05% versus hydrocortisone butyrate cream 0,1%. Data on file, Schering Corp. Kelinworth, NJ. The study received from manufacturer of the drug.
17. Product Information: Aclovate(R), alclometasone dipropionate. Glaxo Wellcome Inc, Research Triangle Park, NC, 2000/1997/1994.
18. Product Information: Aclovate(R), alclometasone dipropionate cream/ointment. GlaxoSmithKline Consumer Healthcare LP, Pittsburgh, PA, USA, 2002.
19. Duchkova H. An increase in skin hydratation following Afloderm 0,05% cream application. Department of Skin Diseases, Masaryk Hospital, Usti nad Labem. Data on file. Belupo, Zagreb, Croatia. The study received from manufacturer of the drug.
20. Duke E et al. Aclometazone diproponate in atopic dermatitis. A clinical study. Curr Therap Res 1983; 33.
21. Bagatell FK, Barkoff JB, Cohen HJ, et al. A multicenter comparison of alclometazone dipropionate cream 0, 05% and hydrocortisone cream 1,0% in the treatment of atopic dermatitis. Curr Therap Res 1983; 33.
22. Lutsky BN, Berkenkopf J, Fernandez X, et al. Selective effects of 7alpha-halogenations on corticosteroid activity: SCH 22219 and SCH 23409. Arzneim Forsch 1979; 29: 992.
23. Aggerwal A, Maddin S. Alclometasone dipropionate in psoriasis: a clinical study. J Int Med Res 1982; 10: 414-8.
24. Frost P, Horwitz SN. Clinical comparison of alclometasone dipropionate and desonide ointments (0.05%) in the management of psoriasis. J Int Med Res 1982; 10: 375-8.
25. Cornell RC, Stoughton RB. Correlation of the vasoconstriction assay and clinical activity in psoriasis. Arch Dermatol 1985; 121: 63-7.
26. Kalivas J, Kanof NB, Miller OF, et al. A controlled clinical comparison of alclometasone dipropionate cream 0,05% and hydrocortisone cream 1,0% in patients with psoriasis. Curr Therap Res 1983; 33: 408-14.
27. Cornell RC. Atrophogenic potential of alclometasone dipropionate ointment 0,05% vs hydrocortisone ointment 1,0%. Curr Therap Res 1986; 39: 260-8.
28. Sharma SD. Efficacy and safety of alcometasone dipropionate 0.05% cream/ointment in 238 patient with steroid-responsive dermatoses. Indian J Dermatol 1988; 33: 56-60.
29. Panja SK, Gangopadhaya AK, Sharma SD. A randomised, double-blind comparison of alclometasone dipropionate 0.05% cream in atopic dermatitis and other dermatoses. Indian J Dermatol 1988; 33: 1-4.
30. Lipozenic J. Clinical opinion on afloderm cream and ointment in treatment of neurodermitis and contact allergic dermatitis. Zagreb, 1991. The study received from manufacturer of the drug.
31. Crespi HG. Topical corticosteroid therapy for children: alclometasone dipropionate cream 0.05%. Clin Ther 1986; 8: 203-10.

32. Lassus A. Alclometasone dipropionate cream 0.05% versus clobetasone butyrate cream 0.05%. A controlled clinical comparison in the treatment of atopic dermatitis in children. Int J Dermatol 1984; 23: 565-6.
33. Lassus A. Clinical comparison of alclometasone dipropionate cream 0.05% with hydrocortisone butyrate cream 0.1% in the treatment of atopic dermatitis in children. J Int Med Res 1983; 11: 315-9.
34. Mobacken H, Hersle K. Alclometasone dipropionate ointment 0,05% versus hydrocortisone ointment 1,0% in children with eczema. Act Therap 1986; 12: 269-76.
35. Kuokkanen K, Sillantaka I. Alclometasone dipropionate 0.05% vs hydrocortisone 1.0%: potential to induce cutaneous atrophy in children. Clin Ther 1987; 9: 223-31.
36. Fitzpatrick DE. Geriatric dermatology. Secrets of dermatology. Binom, Dialects of Neva. 1999; 436-44.
37. Zvezdina IW, Liapow AO, Tereszenko AW. The preparate Afloderm in the treatment of chronic eczema of the elderly people. Moscow state medico-stomatologic university. The study received from manufacturer of the drug.
38. Zvezdina IW, Perlamutrov YN. Effects of external corticosteroid therapy with afloderm preparation on functional parameters of the skin of elderly patients with itching dermatoses. The study received from manufacturer of the drug. http://www.rmj.ru/articles_4500.htm.
39. Morresi A, Simonacci M, Mozzicafreddo G, et al. Alclometasone dipropionate (Legederm) for the treatment of steroid-sensitive dermatoses in the elderly. G Ital Dermatol Venerol 1990; 125: 23-4.
40. Fairley JA, Rasmussen JE. Comparison of stratum corneum thickness in children and adults. J Am Acad Dermatol 1983; 8: 652-5.
41. Brodkin RH, Janniger CK. Common clinical concerns in pediatric dermatology. Cutis 1997; 60: 279-80.
42. Hill CJH, Rostenberg A. Adverse effects from topical steroids. Cutis 1978; 21: 624-8.
43. Thornfeldt C, Cornell RC, Stoughton RB. The effect of alclometasone dipropionate cream 0.05% on the hypothalamic-pituitary-adrenal axis of normal volunteers. J Int Med Res 1985; 13: 276-80.
44. Kabasawa Y, Kanzaki T. Allergic contact dermatitis from alclometasone dipropionate. Contact Dermatitis 1990; 23: 374-5.
45. Reitamo S, Lauerma AI, Förström L. Alclometasone dipropionate allergy. Contact Dermatitis 1991; 25: 78.
46. Isaksson M. Corticosteroid contact allergy – the importance of late readings and testing with corticosteroids used by the patients. Contact Dermatitis 2007; 56: 56-7.
47. Śpiewak R. Alergia kontaktowa – diagnostyka i postępowanie. Alergia Astma Immunologia 2007; 12: 109.
48. Isaksson M, Andersen KE, Brandao FM, et al. Patch testing with corticosteroid mixes in Europe. A multicentre study of the EECDRG. Contact Dermatitis 2000; 42: 27-35.
49. Lepoittevin JP, Drieghe J, Dooms-Goossens A. Studies in patients with corticosteroid contact allergy. Understanding cross-reactivity among different steroids. Arch Dermatol 1995; 131: 31-7.
50. David DS, Berkowitz JS. Ocular effects of topical and systemic corticosteroids. Lancet 1969; 2: 149-51.
51. Neilsen NV, Sorensen PN. Glaucoma induced by application of corticosteroids to the periorbital region. Arch Dermatol 1978; 114: 953-4.