

## CONSENSUS STATEMENT

# Update of the Topical Treatment of Psoriasis

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**Abstract.** Topical therapy continues to be one of the pillars of psoriasis management. Topical corticosteroids and vitamin D analogs are the drugs of choice during the induction phase, and vitamin D analogs continue to be drugs of choice for maintenance therapy. Tazarotene and dithranol are suitable options in patients with certain, specific characteristics. The calcineurin inhibitors can be considered to be second-line treatment for psoriasis of the face and flexures. The efficacy and safety of the fixed-dose combination of betamethasone and calcipotriol in the induction phase is greater than that of either drug alone. The combination of corticosteroids with salicylic acid achieves better results than corticosteroids in monotherapy. None of the drugs evaluated stands out over the others in all clinical situations, and their use must therefore be individualized in each patient and adjusted according to the course of the disease.

**Key words:** psoriasis, topical treatment, therapy.

## REVISIÓN ACTUALIZADA DEL TRATAMIENTO TÓPICO DE LA PSORIASIS

**Resumen.** La terapia tópica sigue representando un pilar fundamental y de actualidad en el manejo de la psoriasis. Los corticoides tópicos y los análogos de la vitamina D son los principios activos de elección durante la fase de inducción, mientras que estos últimos se mantienen como alternativa de elección en el mantenimiento. El tazaroteno y el ditranol resultan alternativas adecuadas en pacientes con determinadas características. Los inhibidores de la calcineurina pueden considerarse tratamientos de segunda línea en la psoriasis de la cara y las flexuras. La eficacia y la seguridad en la fase de inducción de la combinación en dosis fija de betametasona y calcipotriol es superior a la obtenida por ambos principios activos por separado. La combinación de corticoides con ácido salicílico aporta ventajas con respecto a los corticoides en monoterapia. Ninguno de los principios activos evaluados presenta ventajas sobre el resto en todas las situaciones clínicas, por lo que su empleo debe individualizarse para cada paciente y para cada momento evolutivo de la dermatosis.

**Palabras clave:** psoriasis, tratamiento tópico, terapéutica.

## Introduction

With an estimated prevalence of 1.4%, psoriasis is one of the most common motives for consulting a dermatologist in Spain.<sup>1</sup> In recent years, discoveries about the pathogenesis of psoriasis have revolutionized our understanding of the

disease. The most obvious repercussion of these advances in our understanding has been a marked improvement in the quality of treatment with the emergence of a large number of molecules known collectively as biologic agents. It is important to remember, however, that topical therapy is still the only treatment option for approximately 70% of patients (a cohort that coincides more or less with the group of patients with mild to moderate psoriasis) while in the other 30% the condition is largely managed with systemic pharmacotherapy.<sup>2</sup>

Moreover, complete remission is uncommon even in patients with severe forms of the disease who are treated

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with systemic medication. In these patients, topical therapy very often remains part of the treatment regimen as a complement to the systemic therapy.

Thus topical treatment is still a fundamental and very current mainstay in the management of psoriasis. In this context, what is needed is a critical evaluation of the efficiency, efficacy, and safety of the available active ingredients.

## Objectives and Methods

The aim of the present consensus document was to provide up-to-date information about the active ingredients currently available for the topical treatment of psoriasis. Whenever possible, this information has been evaluated according to evidence-based medicine criteria (Appendix 1). However, for mainly historical reasons, appropriate evidence is not available for some of the active ingredients evaluated. It is therefore possible that the conclusions or recommendations made in this document may be altered by the results of future studies. To give greater weight to our main objective, we have minimized discussion of historical aspects and explanations of mechanisms of action in order to pay more attention to the specifically therapeutic aspects of the drugs.

This consensus document was compiled by a panel of dermatologists with experience managing psoriasis, all members of the Spanish Academy of Dermatology and Venereology (AEDV). The clinicians involved work in different clinical settings and parts of the country so that the panel represented most of the different situations found in clinical practice in Spain.

In an initial phase, panel members reviewed the drugs used for the topical treatment of psoriasis according to predefined criteria. A meeting was then held to share the results of these evaluations and to agree on some of the aspects to be assessed and the criteria for standardizing the structure of the document. At the same time, the expert panel also reached consensus on a number of strategies deemed useful in clinical practice, and on others for which the scientific evidence available was inadequate. The conclusions adopted by consensus at this meeting were classified as level III evidence and are shown in the sections entitled "Opinion of the Expert Panel," in a final conclusions section and in the tables. After this draft text had been standardized according to the agreed criteria, it was revised by a committee of experts.

## Topical Corticosteroids

The efficacy and rapidity of action of topical corticosteroids, used for their anti-inflammatory and antiproliferative effects, has made these drugs the treatment most often used to manage mild or moderate psoriasis (Table 1).<sup>3</sup>

## Efficacy

The clinical experience and scientific evidence available supports the use of potent or very potent corticosteroids—especially clobetasol propionate and betamethasone dipropionate—during the initial phase of treatment except on certain sites, such as the face and flexures, where safety is a limiting factor (grade A recommendation).<sup>4</sup> It has been estimated that 75% of cases of plaque psoriasis resolve after 4 weeks of treatment with twice daily clobetasol propionate.<sup>5</sup> Maximum efficacy is reached 2 to 4 weeks after start of treatment, and the improvement obtained can be prolonged with intermittent or even weekly regimens (evidence level II-ii).<sup>6,7</sup> The persistence of clinical remission depends on the potency of the corticosteroid used, and the best results are obtained with clobetasol propionate.<sup>4</sup> In between 20% and 50% of the cases in which the lesions treated have responded favorably within 4 weeks, no rebound flare develops during the following 4 weeks even without maintenance treatment (evidence level I-ii).

## Safety

Topical corticosteroids are considered safe when used for short periods. However, prolonged use of these drugs can cause skin atrophy, perioral dermatitis, striae, and telangiectasia. More rarely, corticosteroid treatment is associated with acneiform eruptions, hypertrichosis, hypopigmentation, ecchymosis, worsening of skin infections, delayed wound healing, and, increasingly often, allergic contact dermatitis. The hypothesis that continued use of topical corticosteroids leads to tachyphylaxis comes from experimental studies but has not been confirmed in clinical practice.<sup>8</sup>

Iatrogenic Cushing syndrome caused by systemic absorption of corticosteroids has been reported, but only very rarely. To prevent such an outcome, the following maximum doses should not be exceeded: 50 g/wk of very potent topical corticosteroids, or 100 g/wk of potent topical corticosteroids. Although no teratogenic effects have been reported in humans, fetal abnormalities have been observed in animals treated with oral corticosteroids. Consequently, topical corticosteroids should be used with care and at the lowest possible dosages during pregnancy.<sup>9</sup>

## Opinion of the Expert Panel

Although the Summary of Product Characteristics generally recommends twice daily application for most drugs, the expert panel agreed with the opinion of a

**Table 1.** Classification of Topical Corticosteroids

<i>Very potent</i>
Clobetasol 0.05% (Decloban, Clovate)
Fluocinolone acetonide 0.2% (Synalar forte)
Halcinonide 0.1% (Halog)
Halometasone 0.05% (Sicorten)
<i>Potent</i>
Betamethasone valerate cream 0.1% (Betnovate, Celestoderm)
Betamethasone dipropionate 0.05% (Diproderm)
Beclomethasone dipropionate 0.025% (Menaderm)
Beclomethasone salicylate 0.025% (Dereme)
Budesonide 0.025% (Demotest, Olfex)
Desoximetasone 0.25% (Flubason)
Diflucortolone valerate 0.05% (Claral)
Fluocinolone acetonide 0.025% (Cutanit)
Fluocinolone acetonide 0.025% (Synalar, Gelidin, Cortiespec, Fluoderma)
Fluocinonide 0.05% (Cusigel, Novoter)
Fluocortolone 0.2% (Utralan M)
Flupamasone (Flutenal)
Methylprednisolone aceponate 0.1% (Adventan, Lexxema)
Mometasone furoate 0.1% ointment (Elocom ung)
Prednicarbate 0.25% ointment (Batmen, Peitel)
<i>Moderate Potency</i>
Betamethasone valerate 0.1% cream (Betnovate, Celestoderm)
Clobetasone butyrate 0.05% (Emovate)
Flumethasone pivalate 0.02% (Locorten)
Fluocinolone acetonide 0.01% (Synalar capilar)
Hydrocortisone butyrate propionate 0.1% (Isdinium, Ceneo)
Hydrocortisone aceponate 0.1% (Suniderma)
Mometasone furoate 0.1% (Elocom cream)
Prednicarbate 0.25% cream (Batmen cream, Peitel cream)
<i>Low Potency</i>
Hydrocortisone 1%, 2.5% (Lactisone, Hydrocortisona Isdin, Schericur)
Fluocortin 0.75% (Vaspit)

At equal concentrations, the potency of the pharmaceutical product is defined by whether the formulation is ointment or cream. Adapted from Miller et al.<sup>8</sup>

number of authors who have suggested that a single daily application is just as effective as the twice-daily regimen, especially in the case of very potent corticosteroids.<sup>4,10</sup> In light of the side effects associated with its prolonged use, strategies for using corticosteroid therapy to treat mild or moderate psoriasis specify daily application of a potent or very potent product for a few weeks followed by a maintenance regimen consisting of several applications during the week or weekend therapy.<sup>11</sup>

## Vitamin D Derivatives

Synthetic analogs of vitamin D are one of the safest and most effective treatments for mild or moderate psoriasis (grade A recommendation). The vitamin D derivatives available in Spain are calcipotriol, tacalcitol, calcitriol.

## Efficacy

In a systematic quantitative review of 37 randomized controlled trials including a total of 6038 patients with moderate plaque psoriasis, the efficacy of calcipotriol was found to be comparable to that of potent corticosteroids after 8 weeks of treatment and better than that of calcitriol, tacalcitol, coal tar, and dithranol (evidence level I-i).<sup>12</sup> The results of several studies that compared calcipotriol with calcitriol and tacalcitol indicated that calcipotriol was more effective, although the differences were small.<sup>13,14</sup>

The beneficial effect has been shown to persist longer with calcitriol than with betamethasone dipropionate. In a multicenter randomized trial of 258 patients, 48% of those treated with calcitriol were still in remission 8 weeks after treatment was discontinued, as compared to 25% of those treated with betamethasone.<sup>15</sup>

The efficacy of vitamin D derivatives was sustained over time, and prolonged use did not give rise to tachyphylaxis.<sup>16</sup>

## Safety

The most commonly reported side effect was irritation on or around the lesion or in certain locations, such as the face or flexures; this occurred in 10% to 20% of cases. Localized irritation is moderately likely in patients taking calcipotriol, limited with tacalcitol, and rare with calcitriol. The likelihood of side effects occurring is decreased by any reduction in the frequency of application or by associating vitamin D analogs with topical corticosteroids. Hypercalcemia and hypercalciuria are possible side effects, but they are rarely found in clinical practice and are associated with weekly doses in excess of the recommended

maximum levels.<sup>17</sup> The risk is higher in pustular and erythrodermic psoriasis. Although calcipotriol is not recommended for the treatment of children under 6 years of age, some authors have observed efficacy and safety results in children similar to those obtained in adults (evidence level II-i).<sup>18</sup>

## Calcipotriol Plus Betamethasone

The calcipotriol/betamethasone dipropionate combination is a cream formulation that contains calcipotriol (50 µg/g) and betamethasone dipropionate (0.5 mg/g), both of which are approved for monotherapy in Europe and the United States of America.<sup>19</sup> This 2-compound product has been shown to be a safe and effective topical treatment for psoriasis (grade A recommendation).

### Efficacy

In 7 double-blind randomized trials including more than 6000 patients, the application of the betamethasone/calcipotriol formulation once or twice daily achieved a mean reduction in the Psoriasis Area and Severity Index (PASI) of between 65% and 74% at 4 weeks (evidence level I).<sup>20-27</sup> These results were significantly better than those obtained with the same regimen of either compound alone irrespective of the excipient used.

Onset of response was rapid, suggesting that a reduction in PASI of more than 50% could be expected at the end of treatment after only 1 week, an outcome that could favor adherence to treatment.<sup>5</sup>

The response observed is independent of the severity of psoriasis (measured using the PASI) at the start of treatment and is not influenced by the patient's age.<sup>28</sup>

Since twice-daily application has not been shown to offer any advantages in efficacy over once-daily application, the latter should be the regimen of choice.

The effect of the 2-compound formulation peaks at the end of the fifth week of treatment, and with daily application can be sustained until the eighth week.<sup>29,30</sup>

The authors of a 52-week study in which the primary objective was to assess the safety of the 2-compound formulation reported that its continuous use obtained a satisfactory response (assessed using the Investigator's Global Assessment of Disease Severity) in a higher proportion of patients than maintenance with once-daily applications of calcipotriol alone (84% compared to 70%).<sup>31</sup> In that study, the treatment was applied as needed.

Because of the rapid response it achieves, some authors have proposed using this combination cream to complement treatment with efalizumab and etanercept to accelerate resolution of lesions and to improve the patient's quality

of life during the interval before the biologic agent achieves its maximum effect (evidence level III).<sup>32,33</sup>

## Opinion of the Expert Panel

In the absence of a definition of "as needed use", the expert panel defined such use as the number of applications per week required to maintain skin lesions under satisfactory control with no more than 1 application a day. In many patients this can be achieved with 3 applications a week (evidence level III).

### Safety

In short-term studies (4 weeks), once-daily application of the 2-compound formulation was associated with an incidence of side effects affecting lesions and adjacent areas of between 3% and 11%, irritation and pruritus being the most common adverse effects.<sup>29</sup> No significant increase in the incidence of adverse effects was observed after 8 weeks of continuous treatment.

No differences were observed with respect to the placebo group in the incidence of either systemic side effects or, when this parameter was measured, in raised serum calcium levels. Consequently, such abnormalities are not expected when the recommended regimen is used with a maximum daily dose of 15 g and weekly dose of 100 g.

In a prospective double-blind randomized trial comparing various treatment regimens over 52 weeks, the incidence of side effects associated with the corticosteroid component of the 2-compound product used during this period was 4.8%, with the most common effects being skin atrophy (1.9%) and folliculitis (1.2%). No significant differences with respect to the side effects that occurred were found between intermittent use—4 weeks of the 2-compound product alternated with 4 weeks of calcipotriol—and monotherapy with calcipotriol.<sup>31</sup>

## Association of Corticosteroids and Salicylic Acid

The combined use of corticosteroids and salicylic acid is based on laboratory studies showing that penetration of topical corticosteroids is increased twofold to threefold when they are administered in conjunction with this keratolytic agent.<sup>34</sup>

### Efficacy

The combination of betamethasone dipropionate 0.05% and salicylic acid 3% obtained a more rapid response than

treatment with clobetasol 0.05% plus calcipotriol 50 µg/g, although there were no significant differences in the final outcomes.<sup>35</sup> It is, however, relevant to note that these studies were based on only small samples and had a number of methodological flaws.

Monotherapy with mometasone furoate has been compared with a combination of mometasone furoate plus salicylic acid in 3 double-blind randomized clinical trials.<sup>36-38</sup> The results of these 3-week studies showed that the combination therapy had an advantage over the single-drug treatment (mean percentage point improvement of the target lesion of 75% as compared to 68%) and more rapidly reduced shedding. None of these studies assessed the course of psoriasis after the study period (grade B recommendation, evidence level I-ii).<sup>44</sup>

## Safety

The adverse events observed in clinical trials were mainly mild or moderate and limited to the areas of application. No adrenal involvement or increases in plasma salicylate concentrations were detected during treatment.<sup>35-38</sup>

The adverse reactions most often reported were burning and itching sensations. Mild signs of skin atrophy were observed in 3% of the patients treated with the 2-compound product. In 1 study, the frequency of adverse events was higher with the combination (20%) than with mometasone alone (13%).

It has been recommended that application of the combination formulation to more than 20% of the body surface should be avoided because of the potential systemic side effects that could be caused by the absorption of salicylic acid, particularly in patients with renal failure.<sup>39</sup> When used in conjunction with phototherapy, the 2-compound product should be applied after the sessions because salicylic acid acts as a photoprotector in the radiation spectrum used.

## Vitamin A Derivatives

Tazarotene is an acetylenic retinoid available in a gel formulation in concentrations of 0.1% and 0.05%. On application to the skin it is converted to the active form, tazarotenic acid.

## Efficacy

Clinical trials of between 6 and 12 weeks duration have shown that once-daily tazarotene 0.05% and 0.1% are effective in improving the clinical signs and symptoms of plaque psoriasis, even in the case of lesions affecting the knees and elbows (grade A recommendation).<sup>40</sup> In a

randomized trial of 334 patients diagnosed with moderate psoriasis, a good response was obtained in 70% of the patients receiving tazarotene 0.1%, as compared to 59% of the patients receiving tazarotene 0.05%, and 35% of those treated with placebo.<sup>41</sup> Once-daily application of tazarotene at either concentration was found to be as effective as twice-daily fluocinonide 0.05% cream, although the latter afforded faster control of erythema (evidence level I-ii).<sup>42</sup> Although the onset of the therapeutic effect was slower than that observed with potent corticosteroids, the response lasted longer after treatment was discontinued (70% response maintained after 3 months).<sup>43</sup>

Tazarotene 0.1% has been reported to have therapeutic effects on onycholysis and pitting in nail psoriasis (evidence level I-i).<sup>44</sup>

The use of moderately potent or potent topical corticosteroids in combination with tazarotene is a good treatment option because the combination accelerates the therapeutic response, minimizes the irritant effect of tazarotene, reduces the corticosteroid dose required, and consequently decreases skin atrophy and the formation of corticosteroid distension striae (evidence level I-ii).<sup>45</sup>

## Safety

Some 20% to 40% of the patients treated with tazarotene develop side effects related to skin irritation: erythema, inflammation, burning sensation, and itching. These side effects are more common with the 0.1% concentration and lead to cessation of therapy in 10% of cases.

## Dithranol

Dithranol or anthralin, a demethylated derivative of chrysarobin that has been used in the treatment of psoriasis for over 100 years, is considered to be a safe and effective treatment of plaque psoriasis (grade B recommendation, evidence level I-ii). However, most of the studies carried out with this drug have significant methodological flaws, presumably for historical reasons.<sup>46</sup>

## Efficacy

In patients with moderate to severe psoriasis, the so-called short-contact regimen (lasting from 15 to 45 minutes) produced a greater than 75% improvement in PASI in 66% of patients at 12 weeks, after a mean treatment period of 72 days.<sup>47</sup> In trials carried out in specialized units where therapy adhered strictly to the recommended regimens, the clinical results obtained with dithranol were comparable to those reported for calcipotriol.<sup>48,49</sup>

The therapeutic effect of dithranol can be enhanced when the drug is used in combination with other antipsoriatic drugs owing to synergies between the different mechanisms of action. Good results, in terms of both efficacy and the duration of the remission, have been obtained when dithranol has been combined with ultraviolet light B (UVB) phototherapy, very potent corticosteroids, and vitamin D analogs.<sup>50-52</sup> However, it is impossible to draw statistically significant conclusions because all of these studies included only small numbers of patients.

## Safety

Systemic toxicity is low because the dithranol molecule barely crosses the epidermis.<sup>3</sup> The chief drawbacks associated with this drug are local irritation—reported in up to 72% of cases in some studies—and the staining, sometimes permanent, of clothing and furniture.

## Opinion of the Expert Panel

Although dithranol is an effective treatment, its management and the side effects it causes tend to limit patient adherence to treatment and consequently the clinical utility of the drug. It should be noted that there are currently no commercial preparations containing dithranol on the market in Spain, so that a preparation has to be made up to order by the pharmacist (magistral formula) if dithranol is prescribed.

## Calcineurin Inhibitors

Tacrolimus and pimecrolimus are nonsteroidal immunomodulators classified as calcineurin inhibitors. Because of their mechanism of action, these drugs have been used successfully in certain types of psoriasis and on certain sites. However, they are no longer approved for this indication (grade B recommendation).

## Efficacy

Since the therapeutic effect of topical tacrolimus and pimecrolimus is limited by the size of these molecules and their scant ability to penetrate the skin,<sup>53,54</sup> these agents are only considered useful in the treatment of psoriasis of the face and intertriginous areas (evidence level II-i).

The authors of the largest study in the literature—a placebo controlled trial including 167 patients—reported an improvement in the outcome measures after 8 weeks of

treatment of 62% in the tacrolimus group as compared to 31.5% in the vehicle group.<sup>55</sup>

Good results have also been obtained with pimecrolimus in the treatment of inverse psoriasis in a double-blind randomized controlled study of 57 patients.<sup>56</sup>

## Safety

Treatment-related side effects should be expected in some 15% of patients; these will include itching, stinging, and erythema at the area of application.<sup>53-56</sup>

## Therapeutic Combinations

In addition to the combination treatments described in the sections on each active ingredient, the usefulness of a number of topical combination therapies for psoriasis is summarized in Table 2.<sup>57-62</sup>

## Conclusions of the Expert Panel

On the basis of the information contributed by the panel members and after the consensus meeting, a series of observations were proposed concerning the efficacy and safety of different therapies in both the induction and the maintenance phase, and recommendations were drawn up concerning the maximum weekly dose, induction and maintenance regimens, and the best topical treatment for special sites. This information is detailed in Tables 3, 4 and 5. Appendix 2 summarizes the mechanism of action, onset of response, and common side effects of each of the topical treatments used to manage psoriasis.

In conclusion, we can summarize the following points:

1. Topical corticosteroids and vitamin D analogs, in both monotherapy and combinations, are the drugs of choice in the management of mild or moderate psoriasis vulgaris during the induction phase. The efficacy and safety of both these compounds have been demonstrated in numerous clinical trials (grade A recommendation, evidence level I-i).
2. Vitamin D analogs are the drugs of choice for maintenance therapy in mild or moderate psoriasis vulgaris (grade A recommendation, evidence level I-i). Topical application of tazarotene is recommended for the treatment of mild or moderate psoriasis. Combining tazarotene with corticosteroids reduces irritation, increases efficacy, and prolongs remission (grade B recommendation, evidence level I-i).

**Table 2.** Proposed Combination Therapies

	Active Ingredient	Synergistic Effect
Topical Combinations	Tazarotene and corticosteroids	Yes
	Calcipotriol and tazarotene	Yes
	Calcipotriol and salicylic acid	None. The calcipotriol is rendered inactive.
	Vitamin D derivatives and corticosteroids <sup>a</sup>	Yes
	Salicylic acid corticosteroids	Yes
Topical medication and phototherapy	Emollients Oleic acid Coconut oil Thick layer Vaseline Salicylic acid in Vaseline	Yes No Contraindicated Contraindicated
	Vitamin D derivatives Calcipotriol and PUVA Calcipotriol and UVB	Yes <sup>b</sup> Yes
	Tazarotene Tazarotene and PUVA Tazarotene and UVB	Yes <sup>c</sup> Yes <sup>c</sup>
	Anthralin Anthralin and UVB Anthralin and PUVA	Yes. Not statistically significant Yes <sup>d</sup>
	Corticosteroids Corticosteroids and UVB Corticosteroids and PUVA	No Yes. Not statistically significant
	Calcipotriol and acitretin	Yes
	Calcipotriol and cyclosporine	Yes. Not statistically significant

Abbreviations: PUVA, psoralen-ultraviolet light A; UVB, ultraviolet light B.

<sup>a</sup>Alternating days or vitamin D derivatives during the week and corticosteroids at the weekend.

<sup>b</sup>Should be applied after sessions or 2 hours before them to avoid inactivation of the product and a burning or stinging sensation.

<sup>c</sup>The doses of UVB and UVA should be reduced to prevent burns.

<sup>d</sup>Poor patient acceptance (unpleasant smell, stains skin and clothing).

3. Monotherapy with a short-contact regimen of dithranol is recommended in patients with mild to moderate psoriasis during the induction phase in specialized clinical settings where treatment is administered according to a precise protocol and assessed continuously (grade B recommendation, evidence level I-ii).
4. A fixed-dose combination of betamethasone and calcipotriol is safer and more effective in the induction phase than either of the constituents alone and reduces the dose of corticosteroid required (grade A recommendation, evidence level I-i). In maintenance therapy, this 2-compound formulation is more effective than vitamin D analogs and equally safe (grade B recommendation, evidence level I-ii).
5. In the acute phase, the efficacy and safety of the combination of corticosteroids and salicylates is greater than that of either of the constituents alone (grade B recommendation, evidence level I-ii).
6. Calcineurin inhibitors can be considered second-line treatments for psoriasis of the face, intertriginous areas, and perianal region (grade B recommendation, evidence level III).

In the interpretation of this review, it should be borne in mind that none of the drugs evaluated stands out over the others in every clinical situation. Furthermore, factors other than efficacy must be taken into account in the choice of treatment. These include safety, comfort, and potential synergies with other topical and systemic treatments, as well as the possibility of reduced efficacy owing to lack of adherence to treatment. The treatment of psoriasis of the nails and scalp has not been evaluated in this document because of the therapeutic peculiarities of these entities.

The present recommendations should be verified and applied on a case-by-case basis for each patient and each

**Table 3.** Considerations and Recommendations on Efficacy, Safety, and Ease of Use

Treatment	Efficacy in Initial Phase	Efficacy in Maintenance Phase	Safety in Initial Phase	Safety in Maintenance Phase	Patient Comfort
Potent corticosteroids	++/+++	+	+++	-/+	++
Vitamin D analogs	++	+++	++	+++	++
Topical retinoids	+	+	+	++	+
Betamethasone/calcipotriol combination	+++	+++	+++	++	+++
Corticosteroids/salicylates combination	+++	-	++	No data	++
Dithranol	++	++	+	No data	-
Calcineurin inhibitors	+	-	++	No data	++

**Table 4.** Induction and Maintenance Regimens and Maximum Weekly Dose

Active Ingredient	Maximum Weekly Dose	Induction	Maintenance	Preferred Use	Observations
Dithranol	No limit	Increasing doses (4–6 weeks)	ND	Induction	Preferably in day hospital
Topical corticosteroids	100 g (Class 1)	1-2 a/day for 2-4 weeks	2-3 a/week	Induction Maintenance	Assess topography and strength
Vitamin D <sub>3</sub> derivatives	100 g calcipotriol, 210 calcitriol, 35 g tacalcitol	1-2 a/day (depending on the drug) 6-8 weeks	1-2 a/day	Maintenance	
Fixed-dose combinations of calcipotriol and corticosteroids	100 g	1 a/day 4 weeks	From 2-3 a/week to 1 a/day	Induction Maintenance	
Combination of corticosteroids and salicylic acid	100 g	1-2 a/day 2-4 weeks	ND	Induction	Localized hyperkeratosis
Tazarotene	100 g	1 a/day 6-12 weeks	ND	Induction	Combine with topical corticosteroids to reduce irritation

Abbreviations: a/day, applications per day; a/week, applications per week; ND, no data.

**Table 5.** Topical Treatment for Special Locations

Location	First Line	Second Line
Scalp	Topical corticosteroids with or without salicylic acid	Calcipotriol
Face	Low potency topical corticosteroids	Topical calcineurin inhibitors
Flexures	Acute: low potency topical corticosteroids. Chronic: tacalcitol, calcitriol	Topical calcineurin inhibitors
Palmoplantar	Potent topical corticosteroids with or without salicylic acid	—

particular stage in the course of the dermatosis, taking into account the clinical history and characteristics of the case and never underestimating personal factors and the

patient's prior experience. The aim is always to optimize the therapeutic potential of the active ingredients while minimizing their disadvantages.

### Conflict of Interest

J.M. Carrascosa has been remunerated by Merck-Serono and Leo Pharma as a speaker, has served as a consultant to Wyeth and Shering-Plough, and has received grants or support for his own research from Merck-Serono.

F. Vanaclocha has been remunerated by Shering-Plough, Abbott, and Leo Pharma as a speaker and has served as a consultant for Janssen-Cilag.

G. Caballé and E. Colomé work for Leo Pharma.

L. Borrego and L. Rodríguez Fernández-Fernández Freire declare no conflicts of interest.

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#### Appendix 1 Criteria Used to Grade the Strength of Recommendations and the Quality of Evidence

Grade A. There is solid evidence to support the use of the drug.

Grade B. There is acceptable/favorable evidence supporting the use of the drug.

Grade C. There is only scant evidence to support the use of the drug.

Grade D. There is considerable evidence against the use of the drug.

Grade E. There is solid evidence against the use of the drug.

The quality of the studies used as evidence for each recommendation is also graded using the following classification:

- I-i. Evidence obtained from at least 1 randomized controlled clinical trial without significant methodological flaws
- I-ii. Evidence obtained from clinical trials with limitations
- II-i. Evidence obtained from nonrandomized controlled clinical studies
- II-ii. While the evidence is not from clinical trials, the results can be clearly extrapolated from observational case-control or cohort studies.
- II-iii. Evidence obtained from case series with or without intervention
- III. Expert opinion based on clinical experience, descriptive studies, and reports of expert panels
- IV. Evidence is inadequate due to methodological problems.

#### Appendix 2. The Mechanisms of Action, Onset of Response, and Common Side Effects of Topical Treatments for Psoriasis

<i>Active Ingredient</i>	<i>Mechanism of Action</i>	<i>Onset of Response to Treatment</i>	<i>Common Side Effects</i>
Potent or very potent corticosteroids (such as betamethasone, mometasone, clobetasol)	Controls inflammation	After 1-2 weeks	Hypopigmentation, skin atrophy, striae
Vitamin D derivatives	Normalizes keratinocyte proliferation and differentiation	After 2 weeks	Irritation, itching, burning sensation, hypercalcemia
Combination of betamethasone and calcipotriol	Controls inflammation. Normalizes keratinocyte proliferation and differentiation	After 1 week	Irritation, itching
Combination of corticosteroids and salicylic acid	Controls inflammation. Enhanced corticosteroid penetration	After 1-2 weeks	Irritation, itching, burning, signs of skin atrophy
Topical retinoids	Normalizes keratinocyte proliferation and differentiation	After 2 weeks	Irritation, itching, burning, stinging, erythema, and desquamation
Dithranol	Antiproliferative effect on epidermal keratinocytes	After 2-3 weeks	Irritation, erythema, staining of the skin and clothes, unpleasant smell
Calcineurin inhibitors	Inhibits activated T cells	After 2 weeks	Burning/stinging, itching