CLINICAL STUDY ON THE EFFECT OF A COSMETIC EMULSION IN IRRITATED SKIN

Sparavigna A.¹, Setaro M.¹, Sormani S.¹, Bergamaschi M.²

¹ Derm Ing Institute for Clinical and Bioengineering Research, Monza (MI) - Italy
² Farmaka S.r.l., Grandate (CO) - Italy
³ Pharmacology Consultant - Farmaka S.r.l., Grandate (CO) - Italy

Received: December, 2002

Key words: Dermatitis; Epidermal barrier; Cutaneous scaling; Hyaluronic acid; Lactoferrine

Summary

The skin is constantly exposed to the environment and therefore is susceptible to a variety of problems among which dermatitis involve an increasing number of people due to environmental aggressive factors and to individual reaction or physio-pathological predisposition. Although the clinical classification of dermatitis is accurate, the identification of factors contributing to the genesis and maintenance of skin disorders is frequently unclear, and this makes the clinical approach to prevention and care of dermatitis sometimes difficult. As a consequence prevention recommendations and pharmacological therapy of dermatitis is frequently unspecific and it includes a number of adjuvant preparations.

KVDS is a cosmetic formulation that has been shown in previous study to be effective as an adjuvant in treating seborrheic dermatitis, and the present study has been undertaken with the aim of assessing its activity and tolerability in other skin disorders. To this end KVDS has been investigated in 20 subjects with atopic dermatitis, and its activity has been evaluated by instrumental cutaneous tests such as skin electric capacitance, TEWL, D-squame and others have been carried out. Its soothing efficacy was also assessed in cutaneous erythema induced by UV irradiation of the skin. The results already reported for seborrheic dermatitis and those obtained in the present study suggest that KVDS might be effective in different types of dermatitis thanks to its beneficial action in improving the cutaneous barrier, to its protective function and its soothing activity.

Riassunto

La pelle è costantemente esposta all’ambiente esterno ed è quindi soggetta a numerosi problemi, tra cui le dermatiti che coinvolgono un numero crescente di persone e possono essere causate da aggressioni di agenti esterni, reazioni individuali o predisposizione fisio-patologica.

Sebbene la classificazione clinica delle dermatiti sia accurata, l’identificazione dei fattori che contribuiscono al loro scatenamento è spesso non chiara, e questo rende difficoltoso l’approccio clinico alla loro prevenzione e cura. Come conseguenza le raccomandazioni per prevenire l’instaurarsi di tali affezioni sono spesso generiche ed il loro trattamento farmacologico include parecchie preparazioni coadiuvanti.

KVDS è una preparazione cosmetica che si è dimostrata efficace nel trattamento della dermatite seborroica, ed il presente studio è stato intrapreso al fine di verificare l’attività e la tollerabilità in altre affezioni cutanee.
Ha coinvolto 20 soggetti con anamnesi positiva per la dermatite atopica, e l’attività della formulazione in studio è stata valutata con test quali la capacità elettrica cutanea, la perdita d’acqua transepidermica (TEWL), la misura della desquamazione cutanea (D-Squame) ed altri. L’effetto emolliente è stato verificato trattando degli eritemi cutanei causati artificialmente mediante raggi UV.

I risultati già riportati per quanto riguarda la dermatite seborroica e quelli ottenuti nel presente studio suggeriscono che KVDS è efficace in vari tipi di dermatiti grazie alla sua azione protettiva, emolliente e di ripristino della barriera cutanea.
INTRODUCTION

The skin is constantly exposed to the environment and therefore is particularly susceptible to a variety of problems among which dermatitis involve an increasing number of people, likely due to raising of pollution and climate alterations on one side and to the strength of the physio-pathological reaction on the other. In addition to chemical and physical factors, a number of health conditions, such as allergies, genetic factors, diet, physical and mental stress can provoke or aggravate dermatitis possibly by altering the normal defensive mechanisms.

The term eczema, or eczematous dermatitis, is applied to specific non-infectious inflammatory reactions of the skin that are dependent on individual predisposition, and covers a number of etiologically heterogeneous conditions with common features in terms of clinical presentation and pathogenesis that account for approximately 20% of the dermatological disorders (2). According to the American Academy of Dermatology, dermatitis affects about one in every five people at some time in their lives, and has an high individual and socio-economical impact.

Dermatitis include skin alterations characterized by swollen, reddened and itchy skin that make people feeling uncomfortable, and the morphology of this skin disorders may vary in the acute or chronic stages, as it is characterized by erythematous and papulo-vesicular aspect when acute, and erythematous and scaling morphology with or without fissures and lichenification when chronic.

By a clinical point of view, the most frequent forms of dermatitis have been classified as: atopic, irritant and allergic, seborrheic and microbic dermatitis (2).

Atopic dermatitis (3) is a chronically relapsing inflammatory skin disease with altered immune and pharmacological responses (4,5). Atopic dermatitis is prevalent in children, it affects approximately 5% of children in Italy, and commonly appears during early childhood (infantile eczema). Inherited factors seem to be of importance, as there is nearly always a family history of dermatitis or asthma, and it often occurs with allergies and frequently runs in families in which other family members have asthma or hay fever. Signs and symptoms include itchy, thickened, fissured skin, most often in the antecubital and popliteal region. Generally, atopic dermatitis symptoms become less serious in adulthood, unless people are exposed to allergens or irritants.

Irritant or allergic contact dermatitis commonly results from direct contact with one of many irritants or allergens causing more trouble in subjects who have a tendency to atopic dermatitis. This includes frequent handling of water, use of common irritants, including laundry and skin soaps, cleaning products, detergents, solvents or harsh chemicals perfume, or of possible allergens, such as rubber, metals, jewelry, perfumes, cosmetics and some weeds. The clinical signs that occur include redness, itching and vesicles, while in severe cases blisters and weeping sores may appear, generally limited to site of contact with the irritant or the allergen. In general it takes a large amount of an irritant over a longer time to cause contact dermatitis, while in people sensitized to a given allergen dermatitis can be caused by just a brief exposure to a small amount of that allergen.

Seborrhoeic dermatitis is characterized by greasy, scaling areas at the sides of the nose, between the eyebrows, behind the ears or over the sternal region, and it can appear as itchy dandruff, usually due to mild seborrhoeic dermatitis of the scalp, or as a “cradle cap”, that is crusty, scaly skin on baby’s scalp. The fact that Malassezia furfur yeast (Pytisporum ovale) plays a part in seborrhoeic dermatitis is well established but the mechanism of the exact relationship has not been established. An increase in inflammatory interleukins, as well as in the regulatory interleukins, in combination with complement activation indicate that an irritant stimulation of the immune system plays an important role in se-
borrheic dermatitis (6). Predisposition to seborrheic dermatitis is often inherited and the disease occurs during periods of psychological stress or in people suffering from neurological conditions such as Parkinson's disease (7).

Microbic or infective dermatitis is provoked by bacterial or fungal infection of particular areas of the skin.

Despite the accurate clinical classification, the identification of the factors contributing to the genesis and maintenance of the skin disorders is frequently unclear, and this makes difficult the clinical approach to the prevention and care of the different types of dermatitis as well as the formulation of strategies for the protection of the skin.

As a matter of facts, with only few exceptions, prevention recommendations and/or protecting procedures are intended for the dermatitis in general, and include: use of suitable soaps, shampoo and detergents; use of suitable clothing; protection of the skin from irritant agents, including dust, solvents, detergents, and from physical injuries; use of emollients, that should be applied with continuity, particularly after bathing and when the skin is itchy; use of moisturizing agents to prevent dry skin.

As far as pharmacological therapy of dermatitis (8,9), is concerned, it includes drugs and preparations that are commonly used for the different types of dermatitis. In fact they include 1) topical steroids, used as cream or ointment that should be applied once or twice daily to the red and itchy areas only for a 5 to 15 day course: different topical steroids may be used either for different parts of the body or for differing grades of dermatitis; systemic steroids are also used; 2) antihistamines preparations are of particular importance for reducing irritation and itching, and particularly useful at night; 4) antibiotics if infection, most commonly caused by Staphylococcus Aureus or Streptococcus Pyogenes, is complicating or causing the dermatitis. Other promising treatments have been introduced quite recently, e.g. topical immuno-modulators with proved anti-inflammatory activity (10). In addition to the mentioned therapies a large number of adjuvant treatments have been introduced so far and contain different active principles.

The present study was undertaken with the aim of investigating the tolerability and the pharmacological activity of a cosmetic emulsion (KVDS*) in skin irritation and atopy.

Materials and methods

Investigations have been carried out in 20 healthy volunteers, 19 females and 1 male aged 13 to 58 years (average 36 years). All the enrolled subjects had clinically diagnosed atopy according to the criteria indicated by Hanifin and Rajka*. Other inclusion criteria and procedures were similar to the first group. Exclusion criteria were the following: pregnancy or lactation, presence of skin disorders in the areas of treatment, systemic pathologies. The study consisted of two sets of experiments:

1- In use skin testing: Each subject applied the product on the right or left deltoid region twice a day, in the morning and in the evening, for 4 consecutive weeks according to a previously defined randomized schedule. At T₀ (basal conditions), T₁ (15th day of treatment) and T₂ (28th day) the clinical examination for tolerability and the following instrumental evaluations were performed:

1) cutaneous hydration (11) (Corneometer CM820, Courage-Khazaka, Köln, Germany) has been evaluated indirectly by evaluating the electrical capacitance of skin surface. In order to reduce the variability of the method, three measures on the same skin area were taken for each volunteer, and the adjusted mean was taken as the hydration value at that time.

2) Trans Epidermal Water Loss (TEWL), i.e. the expression of the epidermal barrier, was mea-

* KVDS is sold as: KOURILES®, SEBODERM®, DERMOPUR® and EMULZE K®
sured by Evaporimeter device (Servo Med, Sweden), and the water loss rate was expressed as the amount of water evaporated per unit area of the skin in the absence of sweating.

3) measurement of the surface lipid content (Derming Tester model STC20, Monza, Italy).

4) measurement of skin surface pH (12) (Skin-pH-meter PH900, Courage-Khazaka, Köln, Germany).

5) cutaneous micro-topography was evaluated by computerized image analysis of skin replicas obtained with a silicon representing the skin surface impression. The subsequent analysis of the cutaneous casts (13,14) was carried out by computerized image elaboration. The pictures, taken with a high-resolution camera, were analyzed through the study of the Fast Fourier Transform and the identification of the mathematical parameter describing the skin micro-relief.

6) D-Squame® for the evaluation of the cutaneous scaling (15) was carried out by taking samples of skin scales from skin surface using a special adhesive tape (D-Squame®, Difa Cooper, Italy). The samples were then submitted to computerized analysis of the image for the measurement of the following parameters: mean area, perimeter, major and minor axes of the scales. Calculation of the respective desquamation index was made according to the following formula:

\[ \text{DI} = \frac{2A + \sum T_\text{s} \times (n - 1)}{6} \]

where \( A \) - is area occupied by the scales (percentage); \( T_\text{s} \) - is the percentage of the scales related to their thickness; \( n \) is the level of scale thickness, scores from 1 to 5.

2- Soothing activity: The soothing efficacy of KVDS has been investigated in 20 volunteers, 18 females and 2 males, aged 13 to 58 years (average: 36 years). whose informed consent had been obtained. For the subjects under 18 a written consent was signed by one of the parents according to previously defined protocol. Among these subjects, 70 % had clinically diagnosed atopy, while 30 % had a positive anamnesis for hyperactivity to sun radiation. Exclusion criteria were the following: pregnancy or lactation, presence of skin disorders in the areas of treatment, systemic pathologies. The skin erythema was induced by ultraviolet radiation of discrete areas of the skin according to Diffey et al. (16). After the minimum erythematous dose (MED) of UV was assessed for each subject, a twice as high dose of UV (2MED) was administered on three well identified, contiguous areas of the skin of the back: an untreated control area, a second pre-treated area, in which KVDS was applied before UV irradiation, and a third post-treated area in which KVDS was applied 24 hours after UV irradiation. KVDS was applied in the fixed amount of 0.1ml per treatment by the same operator, by gentle rotating massage until it was completely absorbed. Clinical score and instrumental evaluation of the erythema index (E.I., by means of optical densitometry (17) were performed at \( T_0 \) (before application) \( T_s \) and \( T_{24} \) (respectively 8 and 24±4 hours from the application of the product).

All instrumental measurements were performed under standard environmental conditions (Temperature 20±2°C, Relative Humidity 45±5%). Before each visit the volunteers were acclimatized under relax conditions for at least 15 min. During 3 hours before the visit, the volunteer had not to smoke, drink coffee or strong drinks and not to use other products on the skin test areas during all the duration of the study. Once verified their distribution, obtained data from instrumental measurements were statistically evaluated using the parametric Student’s “t” test.

Results

1- In use skin testing: The repeated application of KVDS was well tolerated by the subjects in-
cluded in the present study, since neither irritation signs nor dropout occurred during treatment. The results obtained with the instrumental tests can be summarized as follows:

1) the treatment with KVDS did increase the electric capacitance of skin surface (Tab. 1 and Fig. 1) and the recorded values were already significantly increased from 82 to 97 U.A. (p<0.001) at T10 and were still higher than control at the end of treatments (T20 = 93 U.A., p<0.001).

| Table I. Effect of the repeated treatment with KVDS on the electric skin capacitance of 20 subjects with atopic dermatitis. |
|---|---|---|
| n. volunteers. | control (T0) | 2nd week (T10) | 4th week (T20) |
| 20 | AU | AU | AU |
| Mean | 82 | 97 | 93 |
| SEM | 2.01 | 3.17 | 2.95 |
| Student “t” test | p<0.001 | p<0.001 |

1) T0 vs T10; 2) T10 vs T20; AU: arbitrary units

2) The measurement of trans-epidermal water loss (TEWL) allows to objective monitoring of the responses to cosmetic treatments: a marked decrease in water loss rates indicates skin surface occlusion by the treatments, while a shift from high water loss rates to normal rates in subjects with altered skin barrier function likely expresses skin lipid replacement and restored barrier function. Data obtained in the present study and included in Tab 2 (Fig. 2), show that the treatment with KVDS® caused a significant decrease in this parameter compared to the values recorded at T0 (control). In fact mean trans-epidermal water loss values decreased from 6.53 g/m²/h (control value) to 5.73 g/m²/h (p<0.05) at T10, and it was 5.22 g/m²/h (p<0.001) at T20.

| Table II. Effect of the repeated treatment with KVDS on the Trans Epidermal Water Loss (TEWL) of 20 subjects with atopic dermatitis. |
|---|---|---|---|
| n. volunteers. | control (T0) | 2nd week (T10) | 4th week (T20) |
| 20 | g/m²/h | g/m²/h | g/m²/h |
| Mean | 6.53 | 5.73 | 5.22 |
| SEM | 0.35 | 0.35 | 0.25 |
| Student “t” test | p<0.05 | p<0.001 |

1) T0 vs T10; 2) T10 vs T20

3) the treatment with KVDS did not alter the superficial lipid content. In fact the small variations in the mean values relative to this parameter recorded at T10 and T20 did not differ significantly from those recorded at T0;

4) the average skin pH was increased significantly from 6.2 UA to 6.4 (p<0.05) at T10 of treatment, but this change was only transient...
as cutaneous pH was again 6.3 at T20 (Tab. 3).

Table III.
Effect of the repeated treatment with KVDS on the cutaneous pH of 20 subjects with atopic dermatitis.

<table>
<thead>
<tr>
<th>n. volunteers.</th>
<th>control (T0)</th>
<th>2nd week (T1s)</th>
<th>4th week (T20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>IU</td>
<td>IU</td>
<td>IU</td>
</tr>
<tr>
<td>Mean</td>
<td>6.2</td>
<td>6.4</td>
<td>6.3</td>
</tr>
<tr>
<td>SEM</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Student &quot;t&quot; test</td>
<td>p&lt;0.05^1</td>
<td>NS^2</td>
<td></td>
</tr>
</tbody>
</table>

1) T0 vs T1s; 2) T0 vs T20

5) The analysis of the computerized image of skin replicas allows the evaluation of the regularity of skin surface micro-relief and therefore the variations of these characteristics after the use of topical products: micro-relief regularity is elevated in well hydrated skin, while xerotic skin, as that caused by strong detergents, is characterized by a very irregular superficial draw. The computerized analysis of the cutaneous casts carried out in our investigation clearly shows that the treatment with KVDS® did not alter the cutaneous micro-relief. In fact the Fourier spectra of the images of the cutaneous replicas, as the values for X and Y axes obtained at the different experimental times, T0 (control), T1s and T20, were almost unchanged (Tab. 4).

6) The effect of KVDS treatment on scaling resulted in a significant 33 % reduction of the mean scale area at T1s that was maintained at T20, (Tab 5 and Fig. 3), and a significant 37 and 29 % decrease in the mean scale perimeter at T1s and T20 respectively (Tab 5 and Fig.3); reduction of the major and minor axes of the scales were also obtained at the second week of treatment (T30) and maintained throughout the treatment period.

At the same time, the skin desquamation index was significantly reduced from 0.52 to 0.34 after 2 weeks of treatment and it was still 0.37 at the end of treatment (see Tab 6 and Fig 3), thus supporting the previous clinical data concerning the effect of KVDS® on desquamation.

A typical example of cutaneous micro-topography before and at different times of treatment with KVDS T1s and T20 is illustrated in Fig. 4.

Table IV.
Effect of the repeated treatment with KVDS on cutaneous micro-topography in 20 subjects with atopic dermatitis.

<table>
<thead>
<tr>
<th>n. volunteers.</th>
<th>control (T0)</th>
<th>2nd week (T1s)</th>
<th>4th week (T20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>amplitude</td>
<td>amplitude</td>
<td>amplitude</td>
</tr>
<tr>
<td></td>
<td>X-axis Y-axis</td>
<td>X-axis Y-axis</td>
<td>X-axis Y-axis</td>
</tr>
<tr>
<td>Mean</td>
<td>249.9</td>
<td>249.5</td>
<td>234.3</td>
</tr>
<tr>
<td>SEM</td>
<td>133.04</td>
<td>15.3</td>
<td>15.3</td>
</tr>
<tr>
<td>Student &quot;t&quot; test</td>
<td>NS^1</td>
<td>NS^1</td>
<td>NS^2</td>
</tr>
</tbody>
</table>

1) T0 vs T1s; 2) T0 vs T20

Table V.
Effect of the repeated treatment with KVDS on cutaneous scaling (D-Squame test) in 20 subjects with atopic dermatitis.

<table>
<thead>
<tr>
<th>n. volunteers.</th>
<th>control (T0)</th>
<th>2nd week (T1s)</th>
<th>4th week (T20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>area perim.</td>
<td>area perim.</td>
<td>area perim.</td>
</tr>
<tr>
<td>mm</td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
</tr>
<tr>
<td>Mean</td>
<td>136.1</td>
<td>0.59</td>
<td>91.33</td>
</tr>
<tr>
<td>SEM</td>
<td>4.7</td>
<td>0.03</td>
<td>14.4</td>
</tr>
<tr>
<td>Student &quot;t&quot; test</td>
<td>p&lt;0.01^1</td>
<td>p&lt;0.01^1</td>
<td>p&lt;0.05^1</td>
</tr>
</tbody>
</table>

1) T0 vs T1s; 2) T0 vs T20

Table VI.
Effect of the repeated treatment with KVDS on the desquamation index in 20 subjects with atopic dermatitis.

<table>
<thead>
<tr>
<th>n. volunteers.</th>
<th>control (T0)</th>
<th>2nd week (T1s)</th>
<th>4th week (T20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>AU</td>
<td>AU</td>
<td>AU</td>
</tr>
<tr>
<td>Mean</td>
<td>0.52</td>
<td>0.34</td>
<td>0.37</td>
</tr>
<tr>
<td>SEM</td>
<td>0.00</td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Student &quot;t&quot; test</td>
<td>p&lt;0.01^1</td>
<td>p&lt;0.01^1</td>
<td>p&lt;0.05^1</td>
</tr>
</tbody>
</table>

1) T0 vs T1s; 2) T0 vs T20; AU: arbitrary units
Clinical study on the effect of a cosmetic emulsion in irritated skin

Fig. 3 Effect of KVDS on skin scaling.

Fig. 5 Optical densitometry test Changing of the erythema percentage versus T0 (Student's t test: T0 vs. T8 = p<0.01 (control area) and p<0.05 vs. T24 (post treated area))

2- Soothing activity: The application of KVDS significantly reduced the cutaneous erythema at the irradiated skin areas results show a significant reduction of the clinical scores on post-treated areas at T24 (T0 vs. T8 and T24, p<0.05). Regarding the comparison between control and pre-treated areas, a trend towards the reduction in the clinical scores for erythema was detected at T24 also on control area, but this was not statistically significant.

Instrumental evaluation of erythema (optical densitometry): at the level of control area (irradiated and untreated area) a marked, significant 14 % increase of the erythema index (E.I.: p<0.01) was found at T8, while on pre- and post-treated areas the increase was only 5 % (Fig. 5). The soothing activity was particularly evident at the level of post-treated areas at T24 with a statistically significant 9 % reduction of average E.I. (T0 vs. T24, p<0.05).

CONCLUSION

It has recently been published that effective therapeutic agents for dermatitis are limited in number and that they may have long-term toxic side-effects (18). This situation prompted many patients to turn to alternative medical approaches, and the options included over-the-counter (OTC) products (20) so-called natural products or cosmetic preparations as adjuvant treatments. In this study we investigated the therapeutic activity of KVDS®, a cosmetic preparation containing piroctone olamine (Octopirox), hyaluronic acid, Sebomine SB12, oxidative enzymes plus lactoferrin, and Norgel, which was already shown to be effective as an adjuvant in the treatment of seborrheic dermatitis (19,20,21,22) due to its antifungal, antimicrobial and antioxidant activities coupled with an effective moisturizing action. The role of hyaluronic acid (HA) in skin disorders (23) as well as in aging skin (24) is well known and its efficacy in wound healing (25) has been proved in recent clinical investigations. In addition it has been suggested that, due to its physicochemical properties and to the binding to HA receptors, hyaluronic acid might have a value as a novel drug delivery system (26). The antimicrobial activity Octopirox as well as its anti-dandruff activity are well established (27,28). Antimicotic activity has also been reported for Sebomine which contains lactoferrin, a biological protein endowed with antimicrobial (29) fungicidal (30) and antiviral activities (31). Recent studies have also proved that lactoferrin possess anti-inflammatory (32) and immuno-modulating properties(33). Norgel has
been shown to improve skin hydration, an action that is of particular importance in subjects with dry skin. Thus the demonstrated clinical activity of KVDS® on dermatitis seems to be based on the specific activity of each of its components. KVDS® formulation had been showed in previous studies to be effective as an adjuvant in the treatment of subjects with seborrheic dermatitis.

The results obtained in the present investigation confirm the therapeutic effectiveness demonstrated by KVDS® in seborrheic dermatitis, and show that KVDS® is endowed with a remarkable soothing activity in the atopic patients included in the present study. This is accompanied by efficacious hydrating action, significant reduction of trans-epidermal water loss, indicating an improvement of the condition of the cutaneous barrier and improvement of its protective function. Quite interestingly, KVDS® also reduced to a significant extent cutaneous scaling in treated areas.

In conclusion the overall results obtained in our investigation clearly indicate that KVDS® should be advantageously added to the therapeutic armamentarium for atopic dermatitis, as well as for other cutaneous situations in which the changes in skin surface parameters are dependent on the state of hydration, as indicated by changes in electrical capacity, trans-epidermal water loss and surface micro-relief. Moreover, the favorable results previously obtained in seborrheic dermatitis patients and those obtained in the present study in subjects with atopic dermatitis suggest that KVDS® might represent an efficacious tool for the treatment of different types of dermatitis due to its beneficial action in improving the protective function of the cutaneous barrier and to its remarkable soothing activity.
Fig. 4 Typical example of cutaneous micro-topography records obtained before (T0) and during the treatment with KVDS Emulsion (T15 and T30)
References


21) Di Vincenzo R, Sorgani A, Benveniste MJ. (1995) Single blind, controlled, multicenter clinical trial for the evaluation safety, efficacy and compliance of patients using KVDS cosmetic lotion for the treatment of the seborrheic dermatitis of the scalp and face. Comparison vs. a pharmaceutical preparation that is commonly available on the market for the same indication. Farmaka Report from:


Author Address:
Sparavigna A.; Setaro M.: Derming-Institute for Clinical and Bioengineering Research Viale Cesare Battisti,38-20052 Monza (MI)-Italia
Sormani S.; Bergamaschi M.: Farmaka S.r.l.-Via Vetrella,1-22070 Grandate (CO)-Italia