

Sebodiane® DS

Scientific review

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noreva·LED

RECOVER YOUR ORIGINAL SKIN

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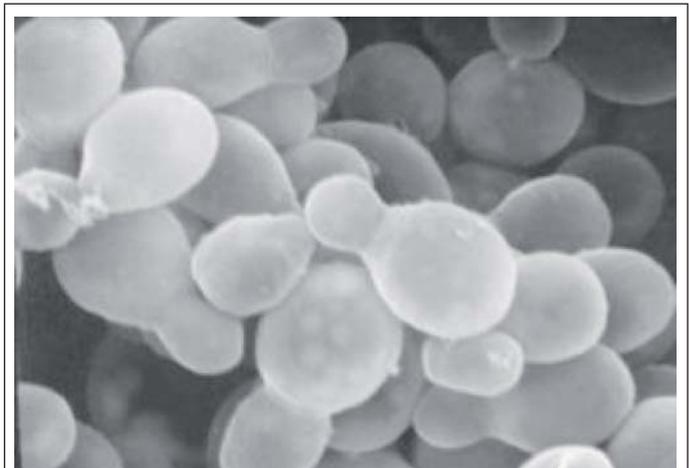
I INTRODUCTION

Seborrheic dermatitis is a common disorder that affects 3 to 5% of the population. It is a common reason for consulting a dermatologist (1-3).

Seborrheic dermatitis occurs in flare-ups, and manifests itself by the appearance of small erythematous desquamative plaques on the sebum-rich areas of the face (border of the scalp, the eyebrows, the area between the eyebrows (glabella), the nasogenian fold and the chin). It is both highly visible and recurrent (5).

Patients experience esthetic and social problems linked to the severity and frequency of flare-ups, and to their possible resistance to treatment (2).

The factors mentioned as probably promoting the development and flare-up of seborrheic dermatitis include: sebum production, *Malassezia*-type yeasts, and external factors, such as periods of stress or weather changes (8, 18, 21, 22).



Malassezia yeasts involved in the development of seborrheic dermatitis.

II EPIDEMIOLOGY AND ETIOLOGY

Seborrheic dermatitis is a common inflammatory dermatitis that occurs in 3 to 5% of the population, mainly in adults (1-2). It accounts for approximately 10% of dermatological consultations (2).

This erythematous-squamous, inflammatory dermatitis is a chronic disorder that occurs via flare-ups (4-5).

Its course changes with age. It is rare before puberty, peaks between 18 and 50 years of age and predominantly affects male subjects (2).

The main functional signs are itching combined with a superficial burning sensation (2).

It manifests itself in the form of red plaques, covered by flakes, which may be pruriginous to varying degrees, and occur predominantly in areas with an abundance of sebaceous glands: the seborrheic areas (5-6). In adults, the facial distribution of the lesions is characteristic: the scalp, eyebrows, the nasogenian fold, and the middle of the chest. It often affects the quality of life of patients who suffer from the disorder (12).

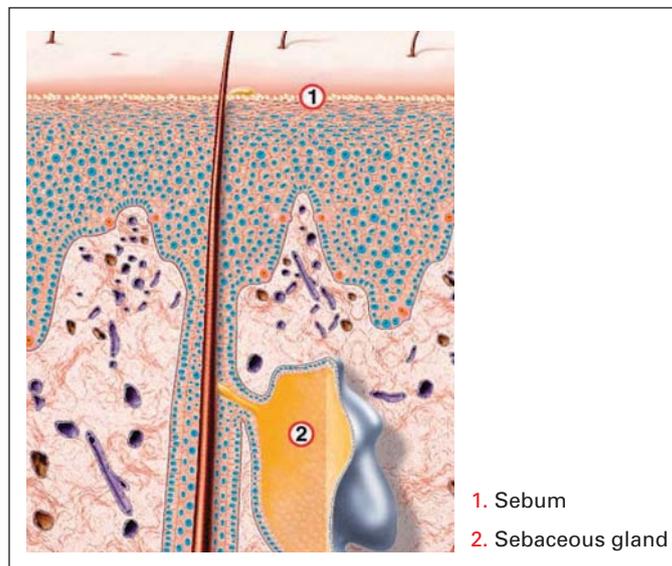
In infants, a similar disorder linked to the genital crisis takes the form of "milk crusts" on the scalp or of nappy rash (16).

This composition of this lipid film changes with age from puberty. When these secretions come into contact with the air, they are oxidized (double bonds of the sphingolipids, fatty acids and squalene derivatives).

Table 1. Composition of human sebum (10-11, 19)

	In the sebaceous gland (%)	On the surface (after hydrolysis of the triglycerides) %
Triglycerides	57	42
Free fatty acids	0	15
Waxes	25	25
Squalene	15	15
Cholesterol esters	2	2
Cholesterol	1	1

Although always known as "seborrheic" dermatitis, the actual role of the sebaceous secretion has not been demonstrated (7-8). Indeed, most patients present with normal levels of sebaceous secretion. Nonetheless, qualitative differences in the sebum have been reported, strengthening the hypothesis that sebum is a triggering factor (7, 29).



The current etiopathogenic theory attributes a permissive role to sebum in all the etiological circumstances of the disorder (7, 12). It probably only plays a secondary, albeit decisive role by promoting the proliferation and accumulation of certain lipophilic and saprophytic yeasts of the skin flora, *Malassezia furfur*, *globosa* and *restricta* (13-15). Yeast lipases

III PATHOPHYSIOLOGY

The pathophysiology of seborrheic dermatitis is complex and multifactorial, involving internal factors such as the sebum (7-14), and external factors such as the flora of the skin (7, 17-28).

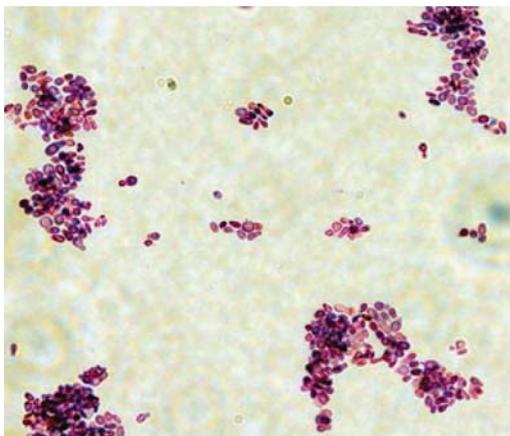
3.1 The role of sebum

Sebum is the group of lipids secreted by the sebaceous glands of the skin. It forms a greasy film that protects the skin against microbes by acidifying it (it contains lactic acid and fatty acids), and confers some degree of impermeability and suppleness to the skin (11).

promote an increase in the quantity of free fatty acids (22-23), which induces an immediate inflammatory reaction that releases cytokines, exacerbating the imbalance of desquamation of the stratum corneum.

3.2 The role of Malassezia

The skin constitutes a huge bacterial and yeast ecosystem (19). The skin surface is colonized by numerous commensal or pathogenic organisms. Some of these are always present, and are known as the resident flora, whereas others are found only transiently: they constitute what is known as the transient flora (14, 19, 22, 27, 28).



Malassezia colonization on the skin surface
(Slide of the skin after rapid staining - Parasitology ENV Alfort)

The resident flora consists of commensal organisms that develop at the expense of the cell metabolism of the host (19):

→ coagulase-negative staphylococci: *Staphylococcus epidermidis*, the main aerobic microorganism in the resident cutaneous flora, *S. warneri* and *S. hominis*;

→ non-diphtherial corynebacteria are present mainly in the skin folds: *Corynebacterium minutissimum* under the armpits, *C. xerosis*, *C. striatum*, *C. tenuis*, *Brevibacterium epidermidis* in the spaces between the toes, which are responsible for the unpleasant odor;

→ propionibacteria: *Propionibacterium acnes*, the main anaerobic microorganism in the resident cutaneous flora, *P. granulosum* and *P. avidum*;

→ yeasts: *Malassezia furfur*, formerly known as *Pityrosporum ovale* or *P. orbiculare*, in the seborrheic areas (28);

→ very numerous species of *Candida*, such as *C. albicans* in warm, damp areas (folds).

The transient flora is made up of the accidental saprophytic organisms of the skin, which they colonize starting with an internal source (nasal, digestive mucosae, etc.) or an external source: *Staphylococcus aureus* (20 to 40% nasal carriage), Gram negative bacilli, such as *Acinetobacter* (*A. johnsonii* and *A. Iwoffii*) and other Enterobacter, group A streptococcus, *Corynebacterium jeikum* and *C. urealyticum*. These microorganism are opportunistic pathogenic bacteria consequently they do not lead to disease except in case of a deficiency of the host or via the particular composition of the host's bacterial ecology.

This cutaneous flora undergoes variation in density ranging from hundreds to millions per square centimeter; the density is low in dry areas and high in areas with large numbers of pilosebaceous units, sweat glands and in the skin folds. It also varies with age (17-19).

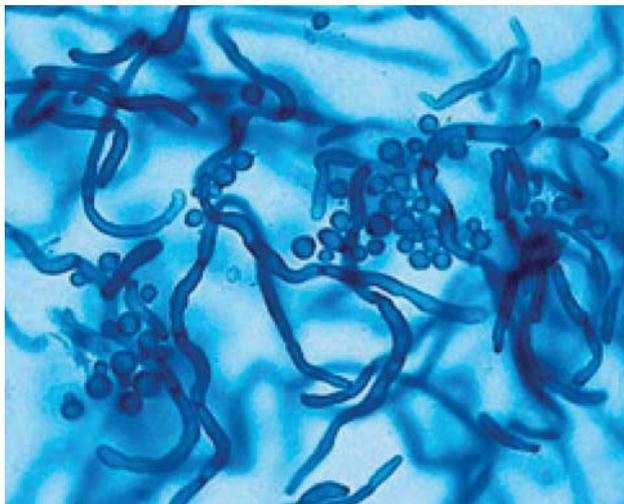
The skin has protective mechanisms to limit its colonization by pathogens and their survival. The flora of the skin varies under certain conditions, playing a protective role versus pathogenic organisms, but can also be responsible for infections in case of overpopulation (20). Under normal conditions, Malassezia are commensal yeasts that are found on the skin of 90% of healthy adults (17).



Malassezia culture on a specific medium

They tend to occur on the scalp, the external auditory meatus, the face, the middle areas of the back and chest, and the pubic areas. The lipophilic nature of these yeasts explain why they tend to occur in areas rich in sebaceous glands, and their keratinophilic nature explains why no lesions occur on the mucosae. Malassezia probably participates in seborrheic dermatitis via an immune and pro-inflammatory mechanism, displaying some degree of proportionality between the density of this flora present in the sebaceous zones, and the clinical severity of the disorder (26).

Yeasts belonging to the *Malassezia* genus are therefore still at the core of the problem (26–28).



Malassezia spp.

Furthermore, other predisposing factors seem to be involved in the onset of this skin disorder (29–32): sweating, cold weather, immunodeficiency notably in the context of HIV (32), neurological status and some endocrine and iatrogenic factors. The condition is exacerbated by emotional stress, and improves spontaneously in the summer.

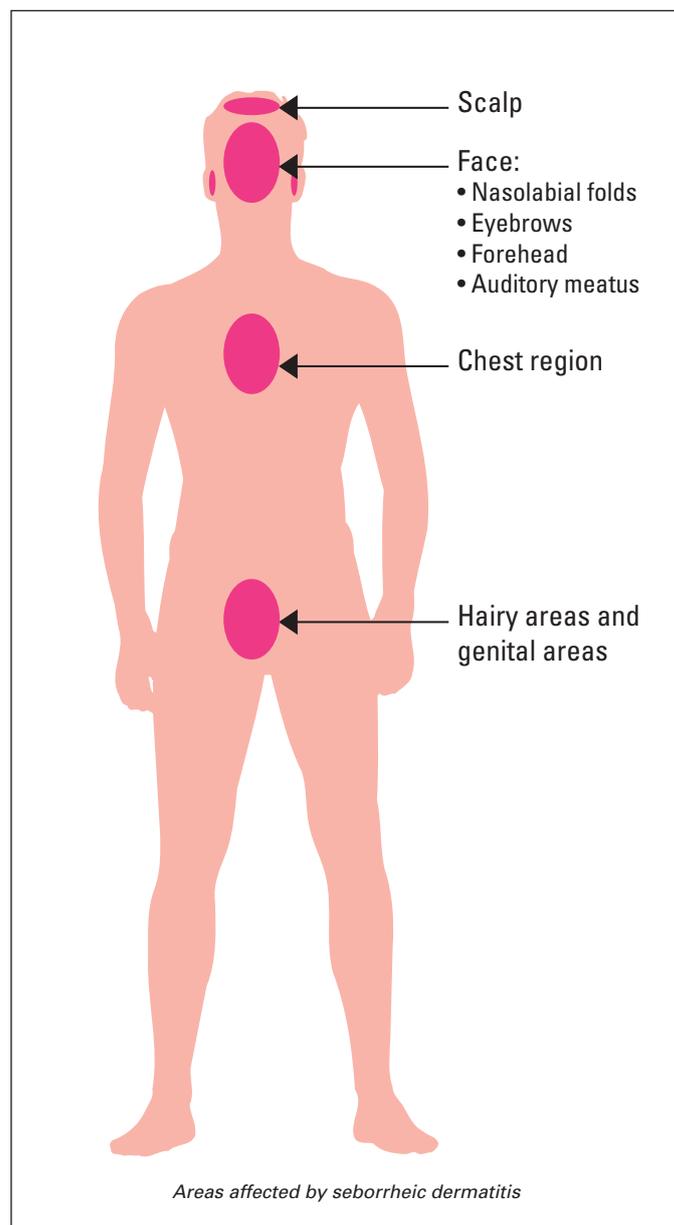
Nonetheless, the lack of information does not allow us to say whether these factors are a predisposing factor for yeast proliferation, or whether they are in fact the primary cause of the desquamation and inflammation.

As a result, in light of current knowledge, the strategies for managing this condition have to attempt to regulate the flora and modulate the inflammatory response by managing the output of sebum.

Things to remember:

1. Seborrheic dermatitis is a very common skin disorder.
2. Seborrheic dermatitis selectively affects sebaceous areas and highly-lipophilic yeasts, the *Malassezia*, play a predominant role.
3. The most common site is the face.
4. Treatment is essentially topical.
5. This is a chronic skin disorder that occurs in the form of flare-ups, sometimes promoted by stress.

IV CLINICAL FORMS (2, 5-6, 33)

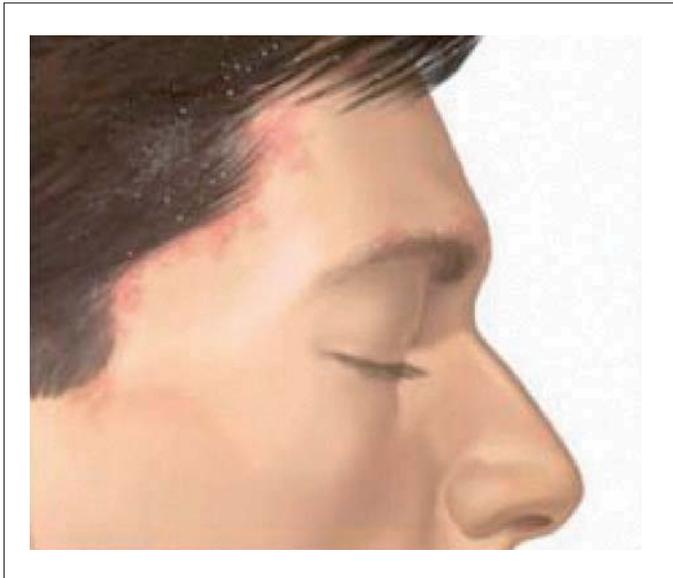


4.1 Facial forms

The face is the most common location of SD. It takes the form of erythematous plaques covered by small, greasy flakes in the areas where seborrhea is predominant: the nasolabial folds, eyelashes, glabella, frontal border of the scalp, etc.

In extensive forms, the chin, and the eyelashes at lid margins may be affected (seborrheic blepharitis).

4.2 Forms affecting the scalp



This can occur in isolation, without involving the face. In mild forms, which are the most common, the scalp is covered by small, non-adhering scales, which as a minimum leads simply to dandruff or pityriasis capitis. In general, the lesions are asymptomatic (pruritus, or even possibly a burning sensation can occur).

In severe forms, there is a cap-like appearance binding tufts of hair (pityriasis amiantacea).

4.3 Forms affecting the trunk

Annular or ring-shaped plaques with scaling edges, typically occurring on the front of the chest (presteral area).

4.4 May affect hairy areas and the genital areas.

Furthermore, depending on the localization, certain clinical forms can be observed and severe and extensive forms can appear more frequently (29–32):

- in patients with Parkinson's disease or iatrogenic extrapyramidal syndromes;
- in chronic alcoholics;
- in patients being treated for carcinoma of the upper aerodigestive tract;
- in HIV-infected patients; the condition occurs in 40% of HIV+ subjects and up to 80% of patients with AIDS.

V TREATMENTS (33,45)

At present there is no curative treatment. Current treatments are in fact only intended to treat the flare-ups. Recurrences are frequent, and are promoted by stress and fatigue. In general, exposure to sunlight and holidays relieve seborrheic dermatitis.

Explain to the patient that:

- this is a chronic disorder and the treatments are intended to obtain a remission and not a permanent cure;
- repeated treatments will be necessary over the long term;
- side effects can result from excessive or inappropriate treatment.

This is a chronic disorder: periods of remission, which may occur with or without treatment, alternate with erythematous-squamous phases.

No treatment provides a permanent cure for this disorder. Topical antifungals are usually prescribed. The use of very "spectacular" corticosteroid therapy (Class II or III) is indicated only for brief periods of time (a few days to control a flare-up), because there is a risk of secondary exacerbation or even corticosteroid dependence.

Unfortunately, the treatments undertaken sometimes have no effect, and the patients resort to self-medication (oils, salt solution, vinegar, etc.), as can be seen from patient forums on the internet.

The therapeutic targets to be considered are:

- reducing the colonization of the skin by *Malassezia*;
- combating inflammation;
- regulating seborrhea.

The aim is therefore to provide treatment that can:

- **limit the symptoms of the condition during flare-ups**
- **reduce the severity and frequency of these flare-ups**
- **make the patient more comfortable.**

On the basis of these criteria, Laboratoires Noreva-led have developed the Sebodiane® DS Line, the first line of sebum-regulating and re-equilibrating products.

VI SEBODIANE® DS

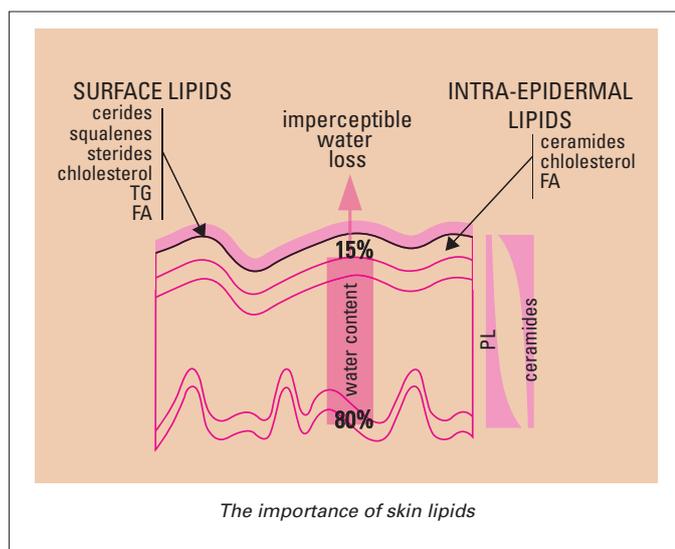
The Sebodiane® DS line is the result of the research and innovation of Laboratoires Noreva-led, and it has been specifically formulated in order to:

- Provide rapid relief from itching and redness
- Get rid of the scales and control yeast proliferation
- Act directly within the sebaceous gland by regulating the quality of sebum
- Control the output of sebum and restore the equilibrium of the skin.

6.1 The active ingredients of Sebodiane® DS

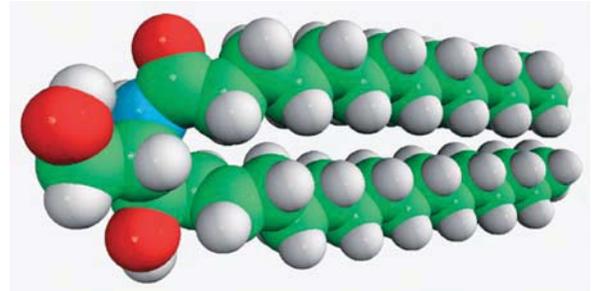
6.1.1 S.Réguline

Lipids, whether in the simple form of triglycerides or that of complex ceramides, are an important constituent of the epidermis.



They play a crucial role in the barrier function of the epidermis, and a major role in anti-microbial defenses (37). In the context of seborrhea and concomitant inflammation, the integration of lipid complexes, which have a configuration similar to that of the lipids naturally present in the skin make it possible to strengthen the innate defenses. As a result, they provide an ecological regulation of the skin flora and maintain skin homeostasis.

It is in this perspective that Laboratoires Noreva-led have combined bioceramides with sterol esters to form S.Réguline. As a result, S.Réguline simultaneously controls the flora of the skin, and has rapid action against inflammatory processes.

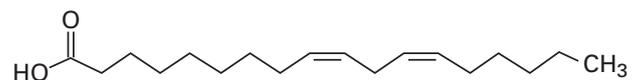


A ceramide (3 D view)

6.1.2 Linoleic acid

Linoleic acid is an essential fatty acid (EFA) that belongs to the omega 6 group. The EFAs have an important structural role in the composition of the stratum corneum: in the composition of cell structures, in its free state and as a predominant constituent of the ceramides, for the regulation of the proteases. EFAs are components of sebum.

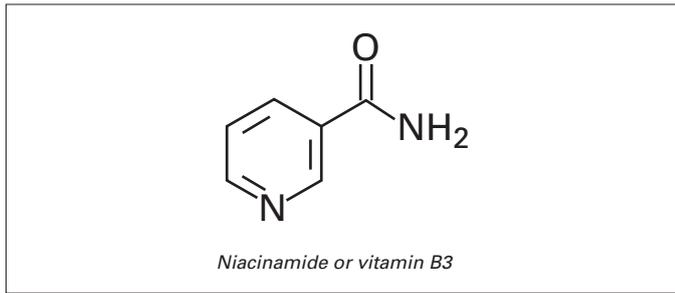
The EFAs also have a functional role because they are an integral part of the membrane lipoproteins. As sources of prostaglandins and leukotrienes, they are involved at various levels in the inflammatory process.



Linoleic acid

Linoleic acid regulates the qualitative composition of sebum, limiting the appearance of free fatty acids. In addition it is a competitive inhibitor of the *de novo* synthesis of the androgens secreted in situ in the sebocytes of the sebaceous gland.

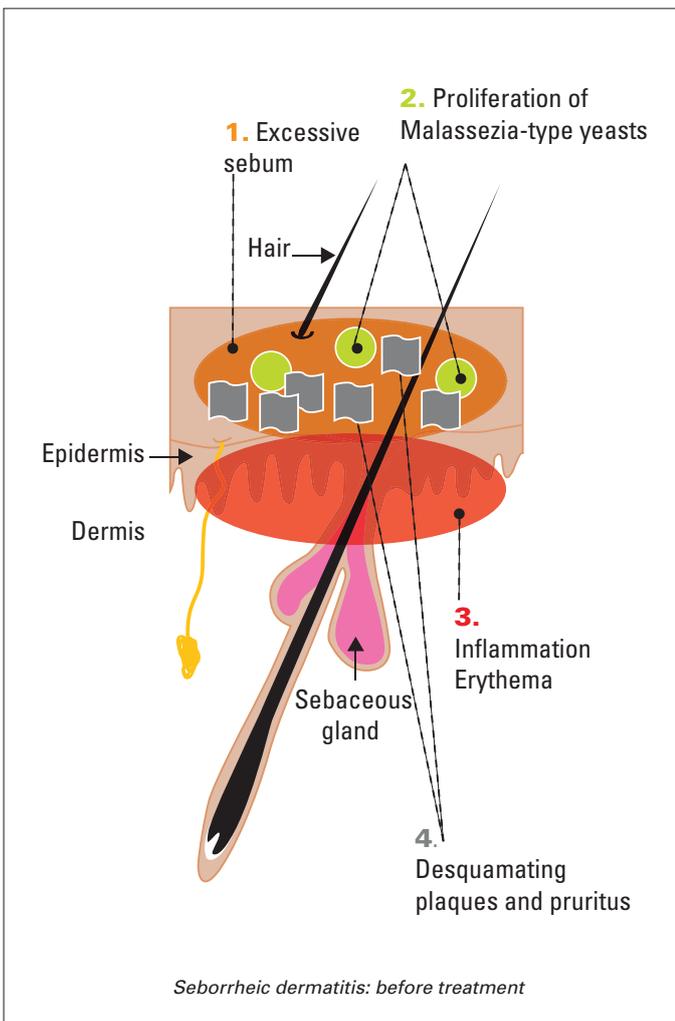
6.1.3 Vitamin B3



Vitamin B3 is an essential amide, and by being integrated as an enzyme-cofactor of serine palmitoyl transferase it increases the *de novo* synthesis of the acyl glucosyl ceramides. This *de novo* synthesis of the ceramides helps to restore the structural equilibrium of the skin.

6.2 Composition of the Sebodiane® DS line

The innovation of the Sebodiane® DS line is based on its mechanism of action: it simultaneously combats both the causes and the consequences of seborrheic dermatitis.



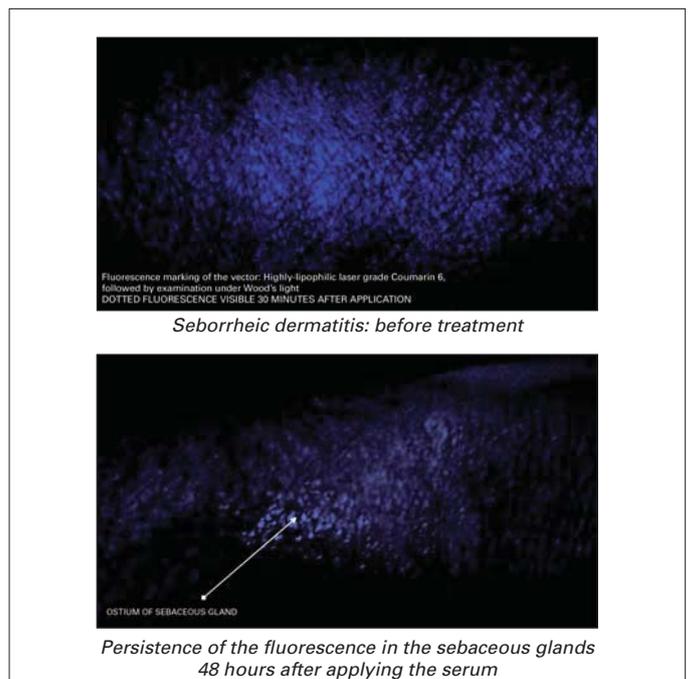
6.2.1 Sebodiane® DS Sérums LP



Sebodiane® DS Sérums LP (Libération Prolongée)

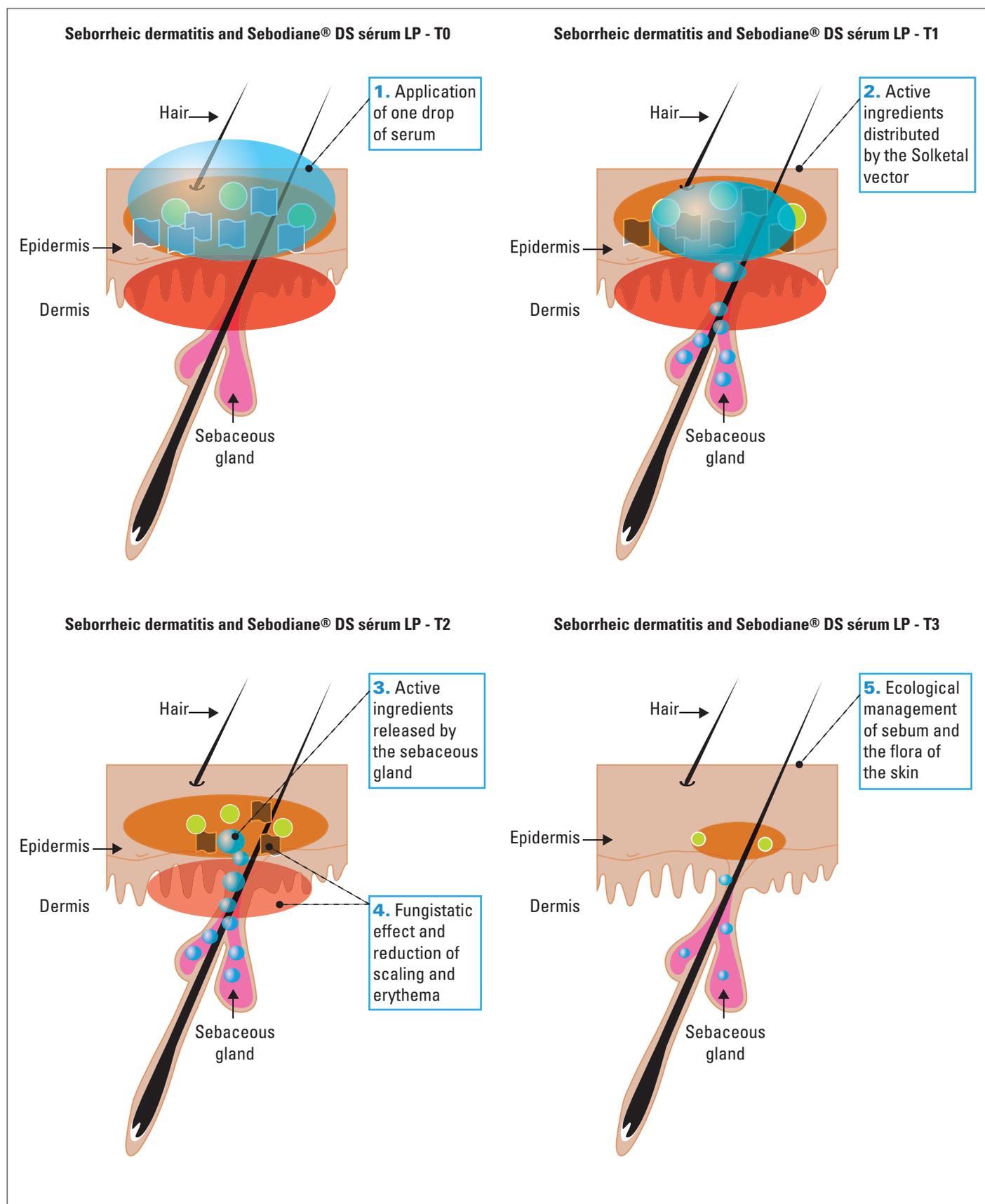
Sebodiane® DS Sérums LP is a true dermatological and pharmaceutical innovation. As a result of its unique vectorization process, this serum makes it possible to ensure maximum, fast and prolonged efficacy acting:

- on the surface, by limiting the proliferation of yeasts, promoting the elimination of the scales and by reducing inflammation as a result of the effect of S.Réguline (40%).
- within the sebaceous gland itself: as a result of its good miscibility with sebum, Solketal (30%), a vector of lipophilic active ingredients, promotes the penetration, storage, and gradual release of S.Réguline and linoleic acid (2.5%), a natural component of sebum. The provision of additional linoleic acid therefore regulates and improves the quality of the sebum whilst controlling inflammation.



Owing to its formulation and its dropper system, the serum has the advantage of offering targeted action

on the affected areas that are the most difficult to reach (hairy areas, auditory meatus, etc.).



6.2.2 Sebodiane® DS Micro-émulsion



Sebodiane® DS Micro-émulsion

6.2.2.1 Characteristics

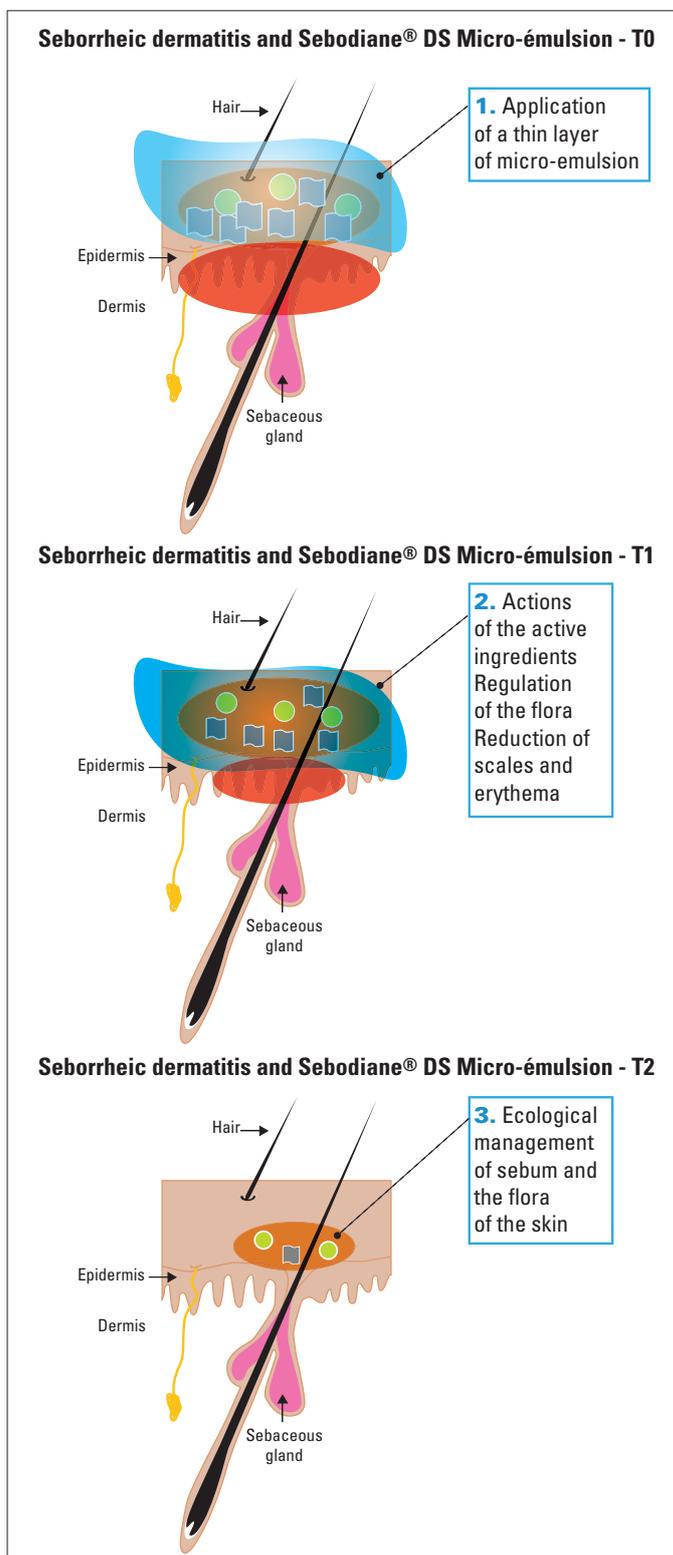
In order to cater to the needs of the most sensitive and irritated skin, Sebodiane® DS Micro-émulsion has been specially formulated to be fragrance-, paraben- and preservative-free. As a result of the synergistic action of S.Réguline, and moisturizing and soothing agents, when this well-tolerated microemulsion is applied to the affected areas, it releases:

- S.Réguline, in order to limit the proliferation of yeasts, to reduce inflammation and to help get rid of the scales,
- Vitamin B3 to control the secretion of sebum and to reinforce the anti-inflammatory effect,
- A complex of moisturizing and soothing agents to provide rapid relief and reconstitute the hydrolipid film of the skin.

Active agent	%	Effect
Emollient and moisturizing complex	18	Relipidizing Moisturizing
S.Réguline	3	Regulation of the skin ecosystem Soothing
Vitamin B3	4	Restructuring

6.2.2.2 Actions

Sebodiane® DS Micro-émulsion rapidly eliminates the sensation of discomfort and tightness, it relieves the itching, and helps to get rid of the scales. Its non-greasy texture provides a real feeling of comfort as soon as it is applied.



6.3 Instructions for use

To treat a severe flare-up:

- In the morning: Sebodiane® DS Micro-émulsion
 - In the evening: Sebodiane® DS Sérum LP
- Apply daily for 10 days
Switch to serum alone 2 or 3 times a week.

Moderate flare-up and/or depending on the zone or surface to be treated:

- Either **Sebodiane® Sérum LP** : once a day for one week, and then twice a week until the lesions have disappeared completely.
- Or **Sebodiane® Micro-émulsion** : once a day for one week and then every-other-day application until the lesions have disappeared completely.

There were no cases of psoriasis, and patients suffering from AIDS were excluded from the trial.

Table 2. Trial subject characteristics.

	Trial 1		Trial 2
	Paris	Tunis	Algiers
n (men-women)	10 (4-6)	10 (6-4)	30 (8-22)
Age (years, mean +/- SD)	45.7+/-15.7	45.7+/-14.8	45.0+/-5.2
Disease duration (years, mean +/- SD)	11.7+/-7.0	8.9+/-4.5	4.1+/-2.0
Previous treatment (%)			
Ketoconazole	50	40	40
Topical corticosteroids	-	30	40
Various antifungals	45	20	10
Others (moisturizers, etc.)	5	10	10
Areas affected (%)			
face	100	100	100
scalp	-	-	20
chest	-	60	13

As Table 2 shows, seborrheic dermatitis is a chronic disorder with a mean duration for its course ranging from approximately 4 to 12 years.

The main treatments used as topical agents before these two trials were KETOCONAZOLE and topical corticosteroids. Followed by METRONIDAZOLE, various anti-fungals and even moisturizing creams.

The following oral agents were used much less frequently (data not shown) KETOCONAZOLE, METRONIDAZOLE and DOXYCYCLINE.

In order of frequency, the lesions always affected the face, then the scalp (including its border) and the chest (in males).

The concomitant illnesses were anecdotal, however diabetes was recorded 4 times in the Professor BOUADJAR's trial.

VII CLINICAL TRIALS TO VALIDATE SEBODIANE® DS

This new Sebodiane® DS concept developed for the active and global management of seborrheic dermatitis has been assessed in two clinical trials:

- Trial 1: a multicenter trial conducted in Paris (Dr. N. AUFFRET, Hôpital Européen G Pompidou) and in Tunis (Prof. DOSS, Hôpital militaire de Tunis), in subjects with ages ranging from 22 to 70 years, with a marked predominance of subjects under 50 years of age.
- Trial 2: the second trial (Prof. BOUADJAR, Dermatology Department, Bab-el-Oued CHU Hospital, Algiers) included 30 patients with recurrent seborrheic dermatitis. The age pyramid was similar, with ages ranging from 20 to 80 years, with a frequency peak between 35 and 55 years of age.

7.1 Protocol for the use of Sebodiane® DS products and results

During both trials, an initial observation was performed on D0 before applying the products, and then after 15 and 30 days of treatment (D15 and D30).

The clinical assessment and its change were assessed by the dermatologist using a scoring system ranging from 0 (no sign) to 5 (very marked signs), for 3 items: erythema, pruritus and scales i.e. giving a maximum possible global score of 15.

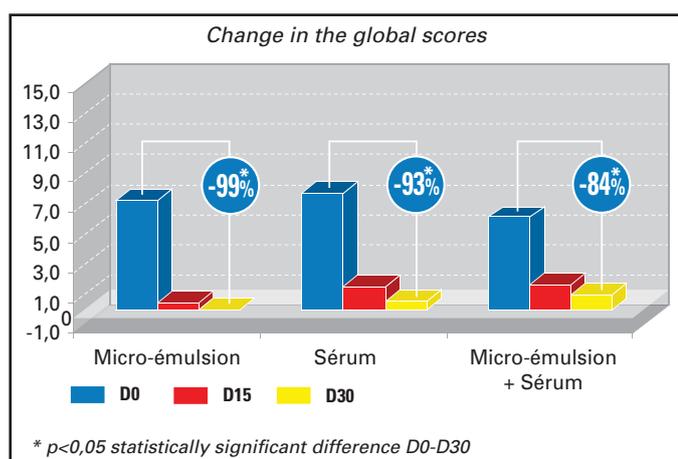
Moreover trial 2, the Sebodiane® DS products were also assessed by the patients.

In each trial, the changes between D0 and D30 were evaluated using a two-sided Student's t-test. A p value of <0.05 was taken to be statistically significant.

7.1.1 Trial 1: Paris and Tunis

Three methods of use for the products were evaluated.

- Group 1 : Microemulsion alone: 2 applications per day for 6 days and then once a day thereafter
- Group 2 : serum alone 2 applications per day for 3 days and then one application per day for 3 days and 2 applications per week thereafter.
- Group 3 : a combination of the two products with the microemulsion in the morning, and the serum in the evening for 3 days and then the microemulsion every morning, and the serum two evenings per week thereafter.



The global scores for all three groups decreased significantly, all with excellent safety and tolerability.

7.1.2 Trial 2 : Algiers

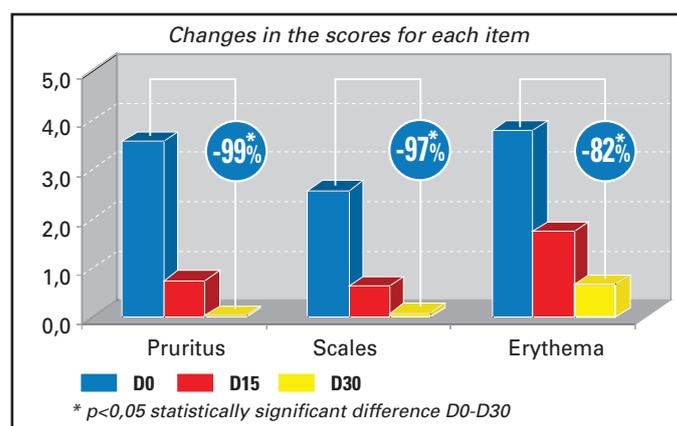
Both Sebodiane® DS products were used according to the following protocol:

Microemulsion in the morning, serum in the evening, for 3 days.

Then Microemulsion every morning, serum two evenings per week for 11 days.

And finally serum alone, twice a week thereafter.

During this trial, 4 patients were lost to follow-up (2 men, 2 women).



Study of the change in scores for each of the items reveals a clear decline.

However, it can be observed that the improvement in the erythema on D15 occurred later than that for the other two criteria (pruritus and scales); but that this former improvement continued until D30, even though only the serum was being used in this last phase.

Assessments by the physician and the patients were both in agreement and excellent (Table 3).

Table 3.: Evaluation and assessment by the patients and physicians of the effects observed with Sebodiane® DS (% positive responses).

		Patients		Physicians	
		D15	D30	D15	D30
Improvement observed	Scales	94	99	90	97
	Pruritus	79	88	73	88
	Erythema	90	98	88	92
Pleasant to use		96	100	-	-
Soothing sensation		96	99	-	-
Ease of use		95	100	-	-

Safety and tolerability was very good apart from 2 cases, which led to the subjects being withdrawn from the trial. These cases concerned females with longstanding and resistant seborrheic dermatitis for which they had received multiple treatments. Mild stinging and burning sensations reported in 5 cases on D15 were no longer present on D30.

The quality of life of all the patients was improved, and described in terms such as "fantastic, impressive, and very satisfied". In all cases, it was emphasized that the treatment was easy to use, and produced a soothing sensation.

7.2 Conclusion from the clinical trials

On D30, both trials demonstrated complete overall control of the seborrheic dermatitis.

- The efficacy of the serum alone should be taken into account given the simplicity of the treatment proposed, and the very limited constraints it involved.
- The microemulsion alone can be used for continuous treatment.
- The combination of the microemulsion and serum is an interesting treatment regimen because it provides immediate comfort and is easy to use.

The results of these trials demonstrate the pertinence and validity of the concept underlying the Sebodiane® DS line in the daily battle against seborrheic dermatitis.

VIII IN CONCLUSION

As a result of its unique dermatological and pharmaceutical approach, the Sebodiane® DS line offers new prospects for the management of seborrheic dermatitis, with improved management of the skin flora, the sebum and consequently, a lasting soothing effect.

The serum seems to provide a good solution for a very simple management of this chronic form of dermatitis. The fact that it is easy to use on hairy areas and in the auditory meatus constitutes a real innovation in terms of the therapeutic armamentarium available today.

The good results obtained using the microemulsion alone or combined with the serum will make it possible to provide a response appropriate for the needs of the most demanding patients or in difficult cases: reactive, intolerant skin and corticosteroid dependency, with a combined efficacy for an optimal result.



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