

## ***n*-Docosanol 10% Cream in the Treatment of Recurrent Herpes Labialis:**

### ***A Randomised, Double-blind, Placebo-controlled Study***

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*n*-Docosanol has been shown to have antiviral activity. To demonstrate the efficacy of *n*-docosanol 10% cream in the treatment of recurrent herpes labialis, a randomised, double-blind, parallel group, placebo-controlled study was undertaken in 63 patients. In a crossover extension, 22 of the patients used the alternative treatment for a further episode. A total of 98 episodes were evaluated. Application of *n*-docosanol 10% cream early in the prodromal or erythema stage of a recurrent episode of herpes labialis shortened mean healing time by approximately 3 days, as compared to late treatment with *n*-docosanol 10% cream and early or late treatment with the placebo. The crossover study revealed that late treatment with *n*-docosanol 10% cream significantly reduced mean healing time compared to placebo. Treatments were well tolerated. **Key words:** antiviral; cold sore; topical application.

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Recurrent herpes labialis ("cold sore") is a common disorder characterised by recurrent vesicle formation on the upper or lower lip, usually near the muco-cutaneous junction. In many cases, recurrences are provoked by exposure to ultraviolet B light (1). While most recurrences are self-limiting and last for only 6–9 days (2), the lesions are generally painful and can cause distressing temporary disfigurement. Early application of an effective topical antiviral agent is expected to shorten the course of the recurrence (2).

*n*-Docosanol, a 22 carbon straight chain-saturated alcohol, exerts substantial inhibitory activity against infectivity and replication of several different lipid-enveloped viruses of both human and animal origin. They include herpes simplex virus subtype 1, which is the commonest cause of herpes labialis (3). The antiviral activity of the compound can be verified in both tissue culture and in experimental *in vivo* models after either topical or systemic administration. *In vitro* studies have demonstrated that *n*-docosanol inhibits the production of herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) as well as certain other lipid-enveloped viruses in cultured Vero fibroblasts and other appropriate target cells (3). *In vivo* studies have shown that the application of *n*-docosanol 10% cream inhibits cutaneous vesicles induced by either HSV-1 or HSV-2 and also hastens healing of established herpes lesions in inoculated hairless guinea pigs (4). Recent observations indicate that the mechanism of action of the drug is that of interference with early post-entry events in the virus target cell replication cycle (4).

This report summarises an evaluation of the efficacy and

safety of a cream containing *n*-docosanol 10% (LIDAKOL™, LIDAK Pharmaceuticals) in the treatment of recurrent herpes labialis in a randomised, double-blind, placebo-controlled crossover study.

#### PATIENTS AND METHODS

The study was conducted in two centres (one in the Netherlands, one in Belgium). Patients with recurrent herpes labialis were recruited through advertisements (placed, for example, in doctors clinics). Those who responded were screened to determine the frequency of recurrent attacks (at least 3 episodes a year were required) and whether they were otherwise suitable for inclusion in the study.

Sixty-three patients, aged 17–60 years, were accepted for the study and had their medical histories taken and underwent laboratory tests. They were briefed about the condition and about the methodology of the study and gave their consent to participate.

Of the 63 patients who entered the first part of the study, 22 also entered into the crossover phase of the study (85 treated episodes). Thirteen (13) patients had a third episode of infection during the study period and therefore used at least one of the study medications to treat two episodes. Therefore, a total of 98 herpes episodes – 48 treated with *n*-docosanol 10% cream, 50 with placebo – were analysed. Of these 98 analysed episodes, only 20 (20%) were classified as "early" treatment initiations, suggesting that a substantial proportion of patients either did not experience prodromes or that these were of very short duration, a papule or vesicle being the first clear sign of a new episode.

Symptom-free patients were allocated at random on a double-blind basis to either the *n*-docosanol or placebo cream. They were instructed to start using the test cream at the first sign or symptom of a recurrence and to continue applying it five times a day until the lesions had healed, up to a maximum of 10 days. Patients kept a daily diary to record the course of their recurrences and the dates and times of treatment applications.

The investigator carried out the first clinical assessment of each of the episodes of recurrence as soon as practicable (on the day that the medication was started or on the first clinic day thereafter). At this assessment the patient was asked about the date and time of the onset of the episode. This, together with information in the patients diary card, allowed the time that the therapy had been initiated to be determined as accurately as possible. The stage of the disease was assessed (prodromes, erythema, papule, vesicle, ulcer, scab, healing, healed), and the length and width of the lesion area were recorded. The initiation of treatment was defined as "early" if it had been started at the prodromal or erythema stage and "late" if started at the papule stage or later. The investigator also ascertained whether or not the treatment was being applied adequately and accurately. The severity of pain, presence of lymph node enlargement, systemic symptoms as well as any adverse events and use of concomitant medication were recorded.

The final assessment by the investigator was made as soon as the lesion was healed. If the lesion had not healed after 10 days of treatment, medication was stopped and the patient was followed up weekly until healing was complete.

Efficacy was measured from the healing time, which was the interval between initiation of treatment and completion of re-epithelialisation. Provided re-epithelialisation was complete, some residual erythema was acceptable. To evaluate the effect that the time of initiating treatment might have on healing time, the results of treatment started early (at the prodromal or erythema stage) and late (at the papule stage or later) were analysed separately from the overall results.

#### Statistics

Statistical analysis of demographic and other background data to check comparability of the treatment groups at baseline was performed using Student's *t*-test and the Mann-Whitney test for parametric and nonparametric data, respectively. Categorical data were analysed using the  $\chi^2$ -test or Fisher's test.

Statistical evaluation of healing time was performed by analysis of variance (GLM) with the factors of treatment (on four levels: *n*-docosanol in early and late treatment and placebo in early and late treatment) to describe the response model. To locate any differences between the treatment groups, a hierarchical system of contrasts was applied, where each difference was tested only in case of a non-significant result in the previous contrast. In addition, the nonparametric Kruskal-Wallis test was applied to confirm the results and to detect any discrepancies in the instance of weakness of the underlying hypotheses of pseudonormality and homogeneity, as supposed in the GLM procedure.

Healing times in the crossover phase of the study were evaluated using GLM with the factors of treatments, periods, treatment initiation (early or late), subjects and the interaction of treatment initiation by treatment to describe the response model.

Laboratory data were analysed using the *t*-test for paired data to detect changes over the treatment course. Changes over the initial course with *n*-docosanol and placebo were compared using Student's *t*-test.

The level of statistical significance was set to  $\alpha=0.05$ , two-sided.

## RESULTS

The treatment groups were found to be well comparable at baseline.

Healing times associated with the first episodes in all patients are summarized in Table I. The analysis of variance showed a significant overall difference between treatment groups ( $p=0.0003$ ). The contrasts according to the hierarchical testing system demonstrated no differences between early and late treatments with placebo ( $p=0.72$ ) and no difference between late treatment with *n*-docosanol and the combined placebo groups ( $p=0.82$ ). Early treatment with *n*-docosanol was found to show significantly shorter healing times compared with all other treatment modalities ( $p=0.0001$ ). The overall mean reduction of healing time was 4.6 days (95% confidence interval 2.6 to 6.6 days).

Healing times observed in the crossover part of the study are summarized in Table II. The number of patients who had treated their lesions early in both parts of the study was too small for a meaningful statistical analysis. However, a substan-

Table I. Healing time (days) of first episodes

	<i>n</i> -Docosanol 10% cream		Placebo	
	Mean $\pm$ SD	(n)	Mean $\pm$ SD	(n)
Early treatment	2.5 $\pm$ 2.4	(10)	6.8 $\pm$ 4.2	(4)
Late treatment	6.8 $\pm$ 3.2	(21)	7.3 $\pm$ 2.7	(28)
All treatments	5.4 $\pm$ 3.6	(31)	7.3 $\pm$ 2.8	(32)

Table II. Healing time (days) of crossover study group

	<i>n</i> -Docosanol 10% cream		Placebo	
	Mean $\pm$ SD	(n)	Mean $\pm$ SD	(n)
Early treatment	2.7 $\pm$ 2.2	(7)	7.0	(1)
Late treatment	5.6 $\pm$ 2.1	(15)	8.0 $\pm$ 2.6	(21)
All treatments	4.7 $\pm$ 2.5	(22)	8.0 $\pm$ 2.5	(22)

tial number had treated their lesions late, thus allowing for intra-patient comparison in this respect.

Comparison of *n*-docosanol and placebo in late treatment revealed a significant difference in favour of *n*-docosanol ( $p=0.03$ ).

When the data from all 98 treatment episodes together are evaluated (single episodes, crossover episodes and additional episodes with the same medication), a statistically significant ( $p=0.02$ ) reduction in mean overall healing time of 1.6 days in *n*-docosanol-treated (5.7 days) versus placebo-treated (7.3 days) patients is revealed. In the subgroup of episodes classified as early treatments (20 in total), topical *n*-docosanol 10% cream reduced mean healing time by 3.3 days ( $p=0.05$ ). Finally, when the effectiveness of early treatment with *n*-docosanol 10% cream was compared to all other treatment modalities combined (late *n*-docosanol 10% cream and early and late placebo), mean healing time in the early treatment *n*-docosanol 10% cream group (3.4 days) differed quite significantly from the range of 6.5 to 7.4 days in the other groups ( $p=0.0002$ ). The differences between late treatment with *n*-docosanol 10% cream and early and late placebo treatment were not significant.

#### Safety and adverse events

No clinically significant differences in laboratory measurements between the active treatment and placebo groups were revealed (i.e. in the changes observed) over the treatment period.

Of the patients completing the study, 3 using placebo reported headache, influenza or a common cold, respectively. Two patients using *n*-docosanol 10% cream experienced a burning or stinging sensation after applying the cream. All these patients completed their treatments. One patient treated with *n*-docosanol 10% cream was withdrawn from the study after 1 day because of a generalised herpes infection in the orofacial area.

## DISCUSSION

In the present study, a cream containing 10% *n*-docosanol produced a highly significant shortening of healing time compared with placebo cream, when treatment was started in the prodromal or erythema stage. When the application of cream in the treatment of first episodes was started after the lesions had appeared, the reduction of healing time lost statistical significance.

The latter observation is in agreement with the findings in several other studies in which the clinical effect of various local treatments was evaluated (5-7). The failure of patients to apply the medication during the very early stage of the outbreak and the lack of sufficient patient numbers were suggested as possible reasons for the discouraging results in

those studies. However, in this group comparative study, the analysis of variance of late treatment results obtained in the crossover component of the study revealed a significant shorter healing time in those patients using *n*-docosanol 10% cream.

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