

Skin hydration and cooling effect produced by the Voltaren[®] vehicle gel

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Background: Voltaren vehicle gel is the carrier substance of the topical Voltaren products. This vehicle gel is especially formulated to be easily applied on the skin, while providing some sensory benefits. The present study aims to substantiate the widely perceived hydrating and cooling effect of Voltaren vehicle gel.

Methods: Volar forearm skin hydration and transepidermal water loss (TEWL) were measured and user satisfaction was evaluated by questionnaires, after application in 31 healthy, female volunteers. The cooling effect was investigated for 40 min with thermal imaging on 12 forearm sites of six healthy subjects.

Results: Voltaren vehicle gel application increased skin hydration by 13.1% ($P = 0.0002$) when compared with the untreated site, 8 h after the final treatment after 2 weeks. TEWL decreased on both treated ($0.37 \text{ g/m}^2/\text{h}$) and untreated ($0.74 \text{ g/m}^2/\text{h}$) forearm sites after 2 weeks (8 h after last treatment), demonstrating a relative increase of 6.5% in water loss. Voltaren vehicle gel application resulted in a rapid reduction of skin surface temperature by 5.1°C after only 3 min with an

average maximum reduction of 5.8°C after 10 min. The cooling effect was experienced by 94% subjects, while 74% felt that their skin became softer. No adverse events, including skin irritation, were reported during the study and by the 37 participants.

Conclusion: This study showed a statistically significant increase in skin hydration as well as a rapid cooling effect lasting approximately 30 min, after application of Voltaren vehicle gel. The small relative increase in water loss may be attributed to an additional skin surface water loss secondary to the increased water content brought into the skin by the Voltaren vehicle gel. The use did not induce any skin irritation and was found acceptable to use by the majority of participants.

Key words: Voltaren – Emulgel – vehicle gel – cooling effect – skin hydration – transepidermal water loss – SSWL

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VOLTAREN VEHICLE gel is the carrier substance of 'Voltaren Schmerzgel' (German trade name) or 'Voltaren Emulgel' (European trade name) containing diclofenac diethylamine 11.6 mg/g (1.16%) as the active drug. This product has been marketed for decades in many countries and was first launched in Europe in 1985, being currently the over-the-counter formulation most commonly used (1). Topical formulations of non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, have been developed to provide analgesia. The specific galenic formulation of the vehicle carrying the NSAID drug, contributes to the drug penetration, tolerability and in addition may affect patient acceptance.

Skin hydration is an important and commonly used parameter to measure moisturizing capac-

ity after the topical application of creams or gels (2). A well moisturized skin not only improves the individual's perception about it but also stabilizes it against environmental influences such as those of a chemical, climatic or bacteriological origin (3–5). Skin hydration measurements using the Corneometer CM 825[®] (6) allow a range to be determined, as the function of the stratum corneum (SC) depends to a large extent on its water content and thus it is widely used in the cosmetics industry to determine relative treatment-induced skin changes (7). The determination of capacitance depends on the electric frequency and on the temperature and structure of the skin surface (8,9). If these are kept constant, an increase in capacitance values correlates with an increase in skin hydration.

Another parameter commonly assessed is the quality of the permeation barrier (skin barrier function) of the SC measured by transepidermal water loss (TEWL), which originally indicated the amount of water vapor passing through the SC by passive diffusion (10–12). TEWL depends on the barrier function of the epidermis as well as on sweat gland activity and thus correctly reflects the SC barrier function only if the skin has a low sweat gland activity.

The cooling effect of a topically applied product can be evaluated using a validated handheld thermal imaging system. When the gel matrix is destroyed after application to the skin, the bound water and alcohol evaporates and a measurable cooling-effect results.

Consumer satisfaction with a topical product is based on subjective criteria such as how the product feels and how it is perceived on the skin. Therefore, appropriate questionnaires are of major importance for cosmetic products to assess the subjective perception not only of soothing and cooling effects but also of moisturizing properties and fragrance.

The aim of this study was to demonstrate the sensory benefits as well as patient acceptance of the Voltaren Emulgel/Schmerzgel diclofenac-free vehicle, by using an objective methodology to determine the cooling and hydrating properties of the vehicle (8, 11, 13, 14).

Materials and Methods

Materials

Study product

The measurements were performed with Voltaren vehicle gel containing no active drug. As the vehicle is the carrier of an approved medicinal product it only contains ingredients that are in compliance with the European Directive 2001/83/EC (15). Ingredients according to INCI declaration: aqua (water), isopropyl alcohol, propylene glycol, paraffinum liquidum, cococaprylate/caprate, cetareth-20, carbomer, diethylamine and perfume.

Study design

This study focused on the cosmetic aspects of Voltaren Emulgel/Schmerzgel vehicle. The larger part of the study was conducted as a randomized, investigator-blinded study in 32 female subjects after a 2-week forearm skin application of Voltaren vehicle gel, in compari-

son with the untreated skin site. The two main read-outs were changes in skin hydration (Corneometer CM 825[®]; Courage & Khazaka electronic GmbH, Köln, Germany) and TEWL (DermaLab[®]; Cortex Technology, Hadsund, Denmark). The smaller part of the study was conducted using an open, uncontrolled, non-randomized, single-dose design in six healthy subjects, where the cooling capacity of the Voltaren vehicle gel was analyzed following cutaneous application to the subject's forearms, using a thermal imaging infrared camera to assess temperature changes. The final measurement was set at 40 min since the pre-application value indicated that the cooling effect was negligible by this time.

Subjective perception of the sensory effect was assessed by all participants using questionnaires.

All subjects were informed about all aspects of the study and provided prior written informed consent. The study was performed according to the principles of Good Clinical Practice following the European Cosmetic Directive 76/768/EEC (16).

Subjects

Skin hydration and TEWL assessments were conducted in 32 healthy females and the cooling effect was assessed in six healthy subjects (three female and three male). Individuals suffering from any skin disease or allergy were excluded from the study. Males were excluded from the skin hydration tests and TEWL because measurement is impaired by hair. Main inclusion criteria were: age between 18 and 70 years with skin phototype I–III without warts, scabs, relevant hairs or tattoos on the test areas. The absence of relevant photosensitivity was a requirement and no systemic anti-inflammatory, antibiotic, corticoid or antihistamine medication was allowed within 1 month prior to inclusion. For the cooling test with the thermal imaging camera no specific criteria for participation were imposed other than the absence of any relevant (skin) diseases.

Method

Skin hydration and TEWL were measured on both volar forearms and on two test sites per forearm following randomization. In all cases

the inner forearm was selected as the testing site because the properties of forearm skin do not seem to differ across gender, age or ethnicity and, therefore, can be considered as an ideal anatomical site for studying the effects of skin products (11, 17).

Skin hydration (corneometry)

A pre-conditioning period of 7 days was allowed before the measurements. No other skin care products and dermatological drugs were permitted to be applied on the arms during that period or during the study. A quantity of 2 mg/cm² Voltaren vehicle gel were applied by the subjects, three times per day for 2 weeks. After 1 week of treatment the compliance of the subjects was checked.

Skin hydration was assessed by 10 repeated measurements immediately before the first application of the product (t_0) and after 2 weeks of application (t_1).

All measurements and procedures were performed in a climate-controlled room at 21.5°C ($\pm 1^\circ\text{C}$) and 50% ($\pm 5\%$) relative humidity after the subjects had acclimatized to these indoor climatic conditions for 30 min. The measurements after application of Voltaren vehicle gel, as well as of the untreated site, were performed at time $t_1 = 8$ h after the last product application.

TEWL (skin barrier function)

During the pre-conditioning period the subjects had to use a special skin cleansing product (shower gel) twice daily on their inner forearms (13, 18). Immediately before the first application of the product (t_0) and after 2 weeks of application (t_1), TEWL was assessed by three repeated measurements on each test site, in pre-defined sequences of 45 s, and was recorded directly by each subject.

Evaluation of cooling properties (thermal imaging infrared camera)

The cooling effect was assessed by infrared thermography in a separated study involving six volunteers, using an infrared camera [FLIR ThermoCam B4 (FLIR Systems, Inc., Wilsonville, OR, USA), Quick Report Software Version 1.2 SP1 (FLIR Systems, Inc)] (19, 20).

Infrared thermography is a noninvasive, contact free temperature measuring technique, which is established for medical use (21–25).

All experiments were carried out in a temperature-controlled room, set at 20°C, 30% relative humidity. To further minimize variations all subjects assembled in the room 30 min prior to testing and stayed there throughout the experiment. A 5 × 8 cm area of skin on the inner side of the forearm was marked and cleaned before product application. Following the determination of the baseline temperature before testing, 0.9 g of the Voltaren vehicle gel were applied uniformly onto the defined areas on each forearm. Measurements were made immediately after and at 1, 3, 5, 10, 15, 30 and 40 min after gel application.

Questionnaires

One week after the start of the skin hydration and TEWL studies the participants were required to assess the sensory properties of the product (moisturizing, cooling, skin smoothening and softening, fragrance and if the product was easily absorbed into their skin) in an interview using a questionnaire.

The six subjects in the investigation of cooling properties study were also asked to complete a subjective assessment questionnaire to assess the ease of application and the sensation after it, the absorption into the skin and the fragrance. The duration of a potential cooling effect was rated by the participants in following categories: 1–5, 5–10, 10–20, 20–30 min or over 30 min.

Statistical evaluation

Data were subjected to descriptive statistical evaluation presented in graphic form where appropriate. For demographic and dosing data, means and medians including their percentages were calculated.

Skin hydration and TEWL

In this study relative data means and standard deviations, distribution of the skin hydration and TEWL (Kolmogorov–Smirnov test) and significance of differences (two-tailed t -test for dependent samples or the Wilcoxon test for paired samples) were calculated. A difference between the treatment situations and the timings of measurement was considered statistically significant if $P \leq 0.05$. With regard to treatment site, skin hydration and TEWL were analyzed for the original data comparing the treated to untreated data and to the t_0 measure-

ment $[(t_1(\text{treated})/t_0(\text{treated})/t_1(\text{untreated})/t_0(\text{untreated}))]$.

Questionnaires

The significance of differences between the treated (Voltaren vehicle gel) and the untreated situation was tested using the *t*-test in the case of normally distributed data, and with the Wilcoxon test in the case of non-normally distributed data for the following comparisons: test sites before product application (t_0) and original data, course of the untreated test sites and original data, product-treated test site in relation to the untreated test site at time t_1 and relative data.

Regarding the subjective assessment, a descriptive statistic was calculated for all questions (number of subjects, mean and frequency distributions). The significance of the correctness of the statements/questions on a five-point-scale was evaluated with the Wilcoxon test for paired samples against a score of +3 (undecided).

Cooling capacity

Minimum and maximum temperatures within defined areas on each right and left forearm were determined. Temperature changes (ΔT) based on the difference between starting temperature (T_0) and measured values at different times (T_{time}), and arithmetic means and associated standard deviations were calculated.

Results

Demographic data

In the skin hydration and the TEWL part of the study, a total of 31 out of 32 subjects aged 49.6 ± 12.5 years (range: 21.5–68.9 years) completed the study and were eligible for full evaluation.

For the investigation of the cooling effect, all six subjects (three females, three males) completed the study. The subjects' mean age was 29.8 ± 1.3 years (range: 29–32 years) with a bodyweight of 83.5 ± 7.2 kg (range: 76–95 kg).

Skin hydration

The original data were normally distributed and measurements of skin hydration were nearly identical at t_0 with or without treatment, averaging (\pm SD) 25.6 ± 6.1 and 25.7 ± 5.4 a.u.

respectively. Results for t_0 and t_1 for both Voltaren vehicle gel administration and no treatment are illustrated in Fig. 1. While the untreated site remained nearly unchanged with a mean of 25.4 ± 6.1 a.u. at t_1 , Voltaren vehicle gel application led to an increase in skin hydration to 28.3 ± 7.5 a.u. Thus, relative to t_0 and untreated, the Voltaren vehicle gel induced a statistically significant increase in skin hydration of 13.1% ($P = 0.0002$) compared to the untreated site after 2 weeks of treatment, 8 h after the last treatment at t_1 .

TEWL

Individual TEWL data at t_0 and t_1 with and without application are illustrated in Fig. 2. TEWL measurements were homogeneously distributed at t_0 , with a mean of 7.94 ± 2.58 g/m²/h (untreated) and 8.08 ± 2.51 g/m²/h (Voltaren vehicle gel). Compared to t_0 levels, both no treatment and vehicle treatment led to a reduction in TEWL to 7.19 ± 1.79 and 7.71 ± 1.92 g/m²/h, respectively. During the study period the TEWL of the untreated site was not homogeneously distributed and showed a statistically significant decrease in TEWL of 0.74 g/m²/h from t_0 to t_1 ($P = 0.0102$). In comparison, changes from t_0 to t_1 after Voltaren vehicle gel application was reduced by 0.37 g/m²/h. However, direct comparison of the data relative to t_0 and untreated for the untreated situation and the use of Voltaren vehicle gel at t_1 resulted in a statistically significant increase of 6.5% in TEWL after the 2-week treatment, 8 h after the final treatment ($P = 0.0405$).

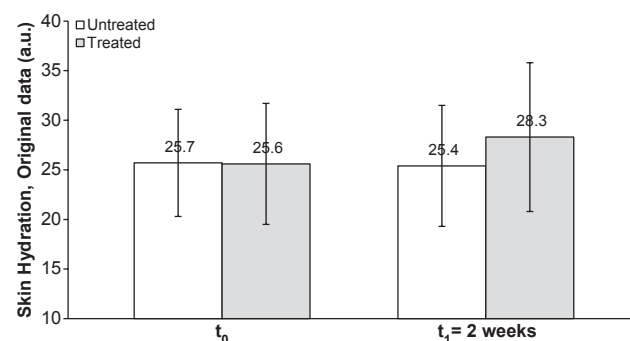


Fig. 1. Original results of skin hydration after 2 weeks, measured 8 h after the last treatment for both Voltaren vehicle gel administration and no treatment. a.u., arbitrary units.

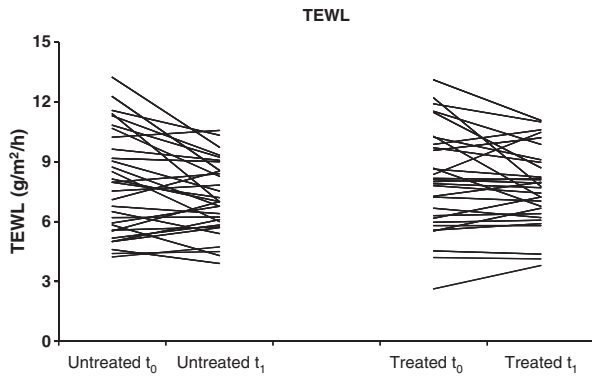


Fig. 2. Individual data on transepidermal water loss (t_0 : before treatment, t_1 : after 2 weeks of treatment/observation).

A total of 13/31 subjects showed an increase in TEWL at time t_1 compared to t_0 on untreated skin sites (range: 0.03–1.47 g/m²/h) compared with 12/31 subjects following treatment with Voltaren vehicle gel (range: 0.10–2.10 g/m²/h). Ten of these 12 subjects showed an increase at both untreated and treated sites.

As can be seen in Fig. 3, there was no clear correlation between the corresponding individual values for skin hydration and TEWL.

Thermographic imaging evaluation of cooling properties

The evaluation of Voltaren vehicle gel's cooling properties by thermographic imaging indicated a significant temperature decrease after gel administration. An example of the thermographic image is given in Fig. 4. Figure 5 shows the mean temperature changes over time. These data demonstrate the cooling capacity of the

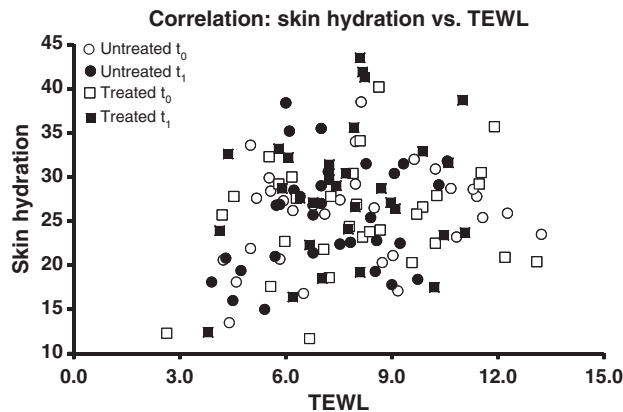


Fig. 3. Correlation between skin hydration and transepidermal water loss (t_0 : before treatment, t_1 : after 2 weeks of treatment/observation).

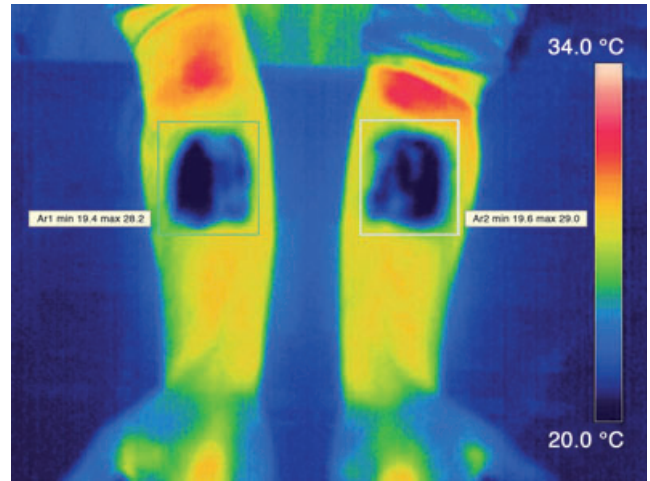


Fig. 4. Example of a thermal image: Subject 04, 15 min after application (Ar1: right forearm; Ar2: left forearm).

Voltaren vehicle gel with a maximum decrease in temperature up to 7.1°C. An average temperature drop of 5.1°C had already occurred after three min, while the average maximum decrease of 5.8°C was achieved after 10 min. The cooling effect started to decrease slowly 15 min after gel application, but was still 3.0°C lower after 30 min ($25.1 \pm 2.43^\circ\text{C}$) compared to the pre-treatment measurements ($28.1 \pm 1.28^\circ\text{C}$).

Subjects evaluation of sensory properties

In the skin hydration and TEWL part of the study, the questionnaire data for the subjective assessment of Voltaren vehicle gel's sensory properties indicated that 29 of the 31 female users (94%) felt a cooling effect after using the gel ($P < 0.0001$) and 65% ($n = 20$) of the subjects rated the cooling effect of the Voltaren vehicle

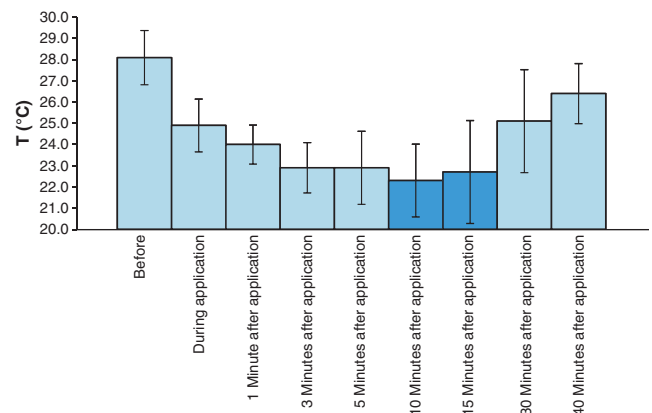


Fig. 5. Mean temperature changes of the skin over time and standard deviations measured by thermographic image.

gel as perfect. Eighty-four percent of the subjects agreed that the vehicle gel was easily applied to the skin ($P = 0.0002$) and 71% of the subjects agreed to the statement that the skin felt smoother after application ($P = 0.0025$). In addition, 52% of the subjects stated that they liked the fragrance of the Voltaren vehicle gel, which was not significantly different from 'neither like nor dislike' user group. Finally, 74% of the subjects felt that their skin became softer after using the Voltaren vehicle gel ($P = 0.0003$).

In the thermographic assessment of the cooling effect part of this study, user subjective evaluation indicated that the Voltaren vehicle gel was easily applied. In addition, the cooling effect was confirmed in the subjective evaluation by the six participants who felt it after 10–20 min, lasting for 10–20 min. Thus the time course of the subjective perception of the cooling effect differed from the objective measurements. The fragrance and the sensation on the skin tended to be rated as neutral.

Tolerability

No adverse events were reported in this study. In particular, no signs of skin irritation were recorded.

Discussion

Voltaren vehicle gel has been used for many decades as the carrier substance of the medicinal product containing diclofenac ('Voltaren Schmerzgel'/'Voltaren Emulgel'). Clinical data have demonstrated the ability of diclofenac from Voltaren Emulgel/Schmerzgel to penetrate deeply through the skin and subcutaneous tissues in order to reach inflamed areas where it exerts its anti-inflammatory and analgesic effects (26). However, the organoleptic properties of the product and their impact on consumer preference have not been widely investigated.

In this study, application of Voltaren vehicle gel resulted in a significant increase of skin hydration by 13.1%. This increase in skin hydration may be attributable to the water, isopropyl alcohol and propylene glycol content (27, 28) in this formulation. Compared to the present study, previous studies using the same methodology generally showed a higher degree of skin hydration of the forearm in an untreated situa-

tion (29, 30). Although Voltaren vehicle gel application resulted in a small but statistically significant increase in the TEWL of about 6.5% compared to the untreated area after a 2-week treatment and 8 h after the last treatment, it needs to be emphasized that overall TEWL results on the treated and untreated sites also showed a clear, albeit small decrease in TEWL. Moreover, Visscher et al. have shown that TEWL increases within just 5 h after the application of formulations containing a natural moisturizing factor on volar forearm skin of healthy subjects, although they significantly decreased TEWL within the first hour after application (31, 32). It was also shown in several studies, reviewed by Lodén (33), that moisturizers usually increase skin hydration without necessarily affecting TEWL (34). Finally, no direct correlation between skin hydration and TEWL was apparent in this study confirming that they are not necessarily directly linked (11, 33).

Transepidermal water loss amounts to water diffusing through the SC from the viable epidermis (true TEWL) and water from the physiological dehydration of corneocytes. These two types of water permeate the intercellular spaces of the SC. It has been clearly demonstrated that the SC has a great affinity for water. When water comes in contact with the skin, it permeates the intercellular spaces, crosses cell membranes and swells the corneocytes. When this exogenous water source is removed, drying takes place. This desorption of water efflux is called skin surface water loss (SSWL) and is distinct from TEWL (35). Both SSWL and TEWL can be directly measured using evaporimetry. Such SSWL has been clearly shown over short period of time through dynamic hydration tests like the sorption-desorption test using water alone (35). It can not be excluded that due to the particular formulation of Voltaren vehicle gel containing water, but also moisturizing agents like propylene glycol, a similar but prolonged SSWL accounts for the relative increase in water loss observed in our study 8 h after the last treatment. This will confirm the previous observations made by Visscher (32). This SSWL would also be fully consistent with the 13% relative increase in SC water content observed with the Corneometer CM 825[®] after 2 weeks of Voltaren vehicle gel administration: it is logical to expect some water efflux from SC after

removal of an exogenous water source as Voltaren vehicle gel for 2 weeks.

For the evaluation of cooling properties, six subjects were considered sufficient to clearly demonstrate the cooling effect of the Voltaren vehicle gel. Very rapidly, already during application, skin temperature decreased and was still 3°C lower after 30 min, indicating a relatively lasting effect. According to the participant questionnaires, subjects felt a cooling effect 10–20 min after Voltaren vehicle gel application, which lasted for 10–20 min on average, indicating that objective measurements and subjective perception of the cooling effect gel differ. Such rapid and relatively lasting cooling effect may be clinically relevant for a gel containing an anti-inflammatory drug with no immediate onset of action. None of the 37 subjects reported any adverse reaction including skin reactions. Although increased skin hydration has been reported as facilitating susceptibility to skin irritants (36), Voltaren vehicle gel does not contain

skin irritating substances in concentrations which could irritate the skin. Any toxicological risk with accidental, improper and/or unforeseeable application of the Voltaren vehicle gel was excluded from previous analyses (37, 38).

Overall, this study utilizing various methods clearly demonstrated that the Voltaren vehicle gel provides a rapid, but also relatively lasting cooling effect upon application and that it also increases skin hydration. Furthermore, the vast majority of users in this study verified that they subjectively experienced the cooling effect of Voltaren vehicle gel and felt their skin became softer and smoother after application. The organoleptic properties of the Voltaren vehicle gel were demonstrated objectively, but also subjectively by the users, which indicate that the product helps to provide certain sensory benefits that could play a role in the perceived efficacy and tolerability of the product and help maintain an acceptable rate of user compliance.

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