Efficacy and safety of cis-trans-1,4-cyclohexanediol gel in the case of adult patients with rosacea, seborrheic dermatitis and facial dermatitis

Skuteczność i bezpieczeństwo cis-trans-1,4-cykloheksanodiolu u dorosłych chorych na trądzik różowaty, łojotokowe zapalenie skóry i zapalenie skóry twarzy

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Streszczenie

Żel zawierający mieszaninę izomerów cis-trans-1,4--cykloheksanodiolu jest nowym preparatem kosmetycznym, przeznaczonym do pielęgnacji skóry z objawami rumienia, grudek, krost i teleangiektazji. Celem badania była ocena skuteczności i bezpieczeństwa stosowania kosmetyku u pacjentów z uciążliwymi zmianami klinicznymi w przebiegu trądziku różowatego, łojotokowego zapalenia skóry twarzy oraz zapalenia skóry twarzy z rumieniem i teleangiektazjami. Badaniem objęto grupę 40 pacjentów spełniających kryteria włączenia. Oceny klinicznej dokonywano podczas wizyty inicjującej oraz po 7, 14 i 21 dniach od rozpoczęcia badania. Ocenie poddano nasilenie występowania rumienia, nacieku zapalnego, grudek, krost oraz teleangiektazji, a także objawów subiektywnych, takich jak świąd czy pieczenie skóry. Obserwowana poprawa skóry w zakresie wszystkich badanych parametrów była istotna statystycznie. Nie obserwowano natomiast klinicznie istotnych działań niepożądanych badanego preparatu. Należy zatem uznać, że 1,4-cykloheksanodiol jest substancją skuteczną i bezpieczną w codziennej pielęgnacji skóry wrażliwej, zmienionej zapalanie w przebiegu trądziku różowatego, łojotokowego zapalenia skóry twarzy czy dermatitis perioralis.

Słowa kluczowe: *1,4-cykloheksanodiol, trądzik różowaty, łojotokowe zapalenie skóry, dermatitis perioralis.*

Abstract

Cis-trans-1,4-cyclohexanediol is a component of a new skin care gel for use in the treatment of skin conditions associated with inflammatory, erythematous, papulopustular and teleangiectatic skin lesions. The aim of the study was to evaluate the efficiency and safety of this product in the treatment of skin inflammation in rosacea, seborrheic dermatitis and facial dermatitis of adults. We investigated forty subjects who were evaluated in terms of clinical score (erythema, papules, pustules, teleangiectasia, and additionally itching and burning sensation) at baseline, and after 1, 2 and 3 weeks of treatment. We recorded a significant improvement of the global clinical score and a reduction of the itching and burning sensation. We did not observe any clinically relevant side effects of the treatment. Therefore, we suggest that 1,4-cyclohexanediol gel is a safe and effective cosmetic for everyday skin care, and especially for the treatment of skin conditions associated with skin inflammation in rosacea, seborrheic dermatitis and facial dermatitis.

Key words: *1,4-cyclohexanediol, skin inflammation, rosacea, soborrheic dermatitis, perioral dermatitis, face dermatitis.*

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Introduction

Skin diseases can significantly affect a subject's appearance. Therefore, they have an important impact on quality of life, especially on its social and emotional aspects [1, 2]. Rosacea, seborrheic dermatitis, and other inflammatory skin conditions characterized by facial erythema and teleangiectasia definitely belong to such skin conditions. Numerous cosmetic and pharmaceutical companies are actively working on improvements to extend the range of products used for the treatment of such cases. Cis-trans-1,4-cyclohexanediol* is the newest innovation of Cinna Health Products, Cincinnati, USA (a division of the Molecular Research Center) [3]. It is a skin care gel intended for use as a cosmetic for everyday use to improve the appearance of sensitive skin with signs and symptoms of inflammation. The aim of the study was to evaluate the efficiency and safety of 1,4-cyclohexanediol gel as a cosmetic applied to improve skin appearance in rosacea, seborrheic dermatitis and face dermatitis in adults.

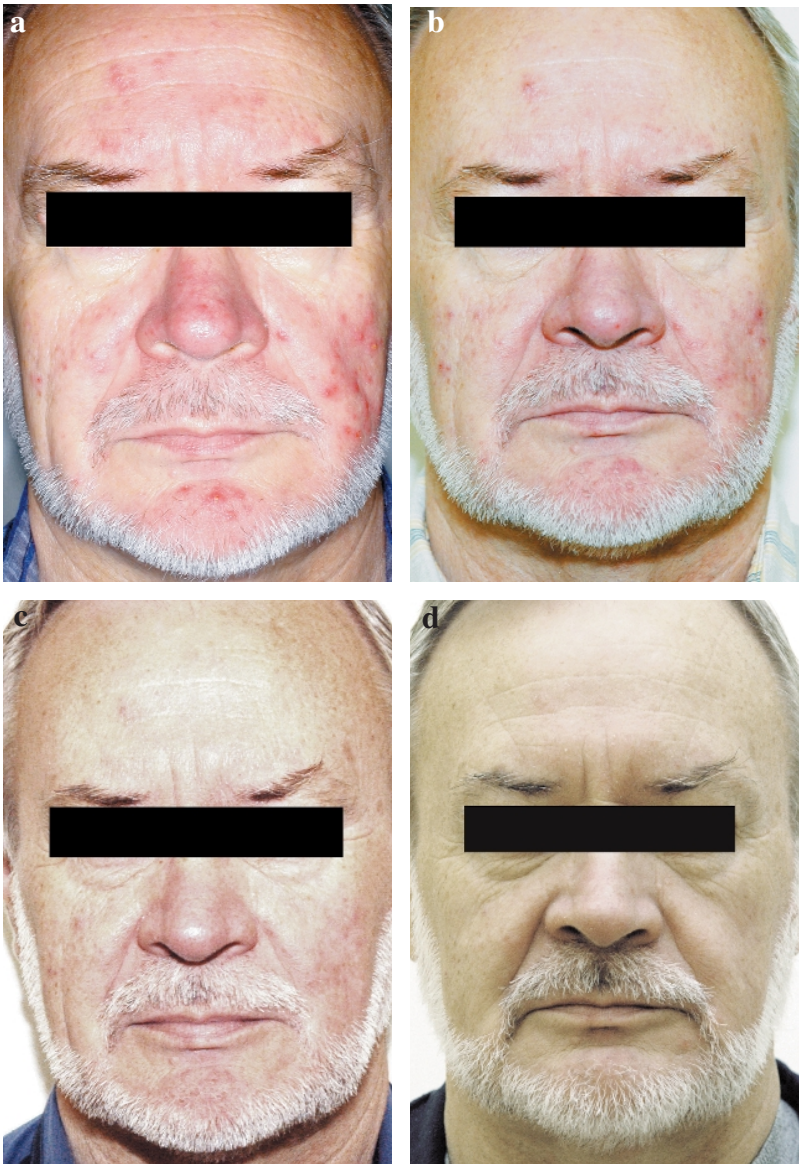


Figure 1a. Subject using 1,4-cyclohexanediol gel – baseline
Figure 1b. Subject using 1,4-cyclohexanediol gel – visit 2 after 7 days
Figure 1c. Subject using 1,4-cyclohexanediol gel – visit 3 after 14 days
Figure 1d. Subject using 1,4-cyclohexanediol gel – visit 3 after 21 days

Subjects

Forty subjects aged 22 to 66 years (mean ±SD 43±13 years) were enrolled in this study: 34 female (mean age ±SD 43±14 years) and 6 male (mean age ±SD 40±10 years). Seventeen subjects were affected by seborrheic dermatitis, 14 by rosacea, 5 by perioral dermatitis and 4 by face dermatitis. The study inclusion criteria comprised men and women older than 18 years old with diagnosis of rosacea, seborrheic dermatitis or facial dermatitis with erythema and teleangiectasia lasting at least 6 months after establishment of the diagnosis. Women of childbearing potential were obligated to use at least one method of contraception. Additionally, the subjects were asked to sign an informed consent agreement before the study and related procedures were started. Exclusion criteria comprised: subjects who did not meet the inclusion criteria, women who were pregnant, breast feeding or planning a pregnancy during the study period, subjects who had used a topical treatment within two weeks prior to the study, subjects who received systemic anti-inflammatory treatment within 4 weeks prior to the study, subjects with another skin condition or severe concomitant systemic disease which could impact the study results, subjects treated with investigational drugs within 2 months prior to the study and subjects with psychiatric disorders.

Study design

The subjects used 1,4-cyclohexanediol gel twice daily for 3 weeks.

Table 1. Evaluation of product efficacy in skin appearance tests at the end of the study (day 21)

	Study group [n=39]		Seborrheic dermatitis [n=16]		Rosacea [n=14]		Perioral dermatitis [n=5]		Face dermatitis [n=4]	
	Doctor's opinion	Subject's opinion	Doctor's opinion	Subject's opinion	Doctor's opinion	Subject's opinion	Doctor's opinion	Subject's opinion	Doctor's opinion	Subject's opinion
I	4	6	4	5	–	1	–	–	–	–
II	29	22	10	8	10	7	5	5	4	2
III	5	7	1	–	4	5	–	–	–	2
IV	1	4	1	3	–	1	–	–	–	–
V	–	–	–	–	–	–	–	–	–	–
Total	39	39	16	16	14	14	5	5	4	4

I – clearance of symptoms, II – definite improvement, III – slight improvement, IV – no effect, V – worsening

The gel was applied after cleansing the skin with warm water. Evaluation of dermatological status was performed at the baseline and after 7, 14 and 21 days of gel application. Skin appearance and lesions such as erythema, inflammation, papules, pustules and teleangiectasia were evaluated using a 4-point severity score (0 points – clear of skin lesions, 1 point – mild, 2 points – moderate, 3 points – severe, 4 points – very severe). Additionally, evaluation of pruritus and burning sensations was performed (0 points – no symptoms, 1 point – mild exacerbation, 2 points – moderate exacerbation, 3 points – severe exacerbation). During the final visit, assessment and self-assessment were performed by clinicians and subjects respectively, in order to evaluate the efficacy of the investigated product (1 point – clearance of symptoms, 2 points – definite improvement, 3 points – slight improvement, 4 points – no effect, 5 points – worsening). Furthermore, any adverse events or concomitant therapy were recorded throughout the study period.

Statistical analysis

The Friedman ANOVA test for multiple dependent samples was used to compare differences between all four visits. The level of significance of the differences between every two visits was checked with the Wilcoxon test for two dependent samples. The Spearman rank-order correlation was used for testing the agreement of subjects and doctors' evaluations of efficacy of the product. A p value lower than 0.05 was considered significant.

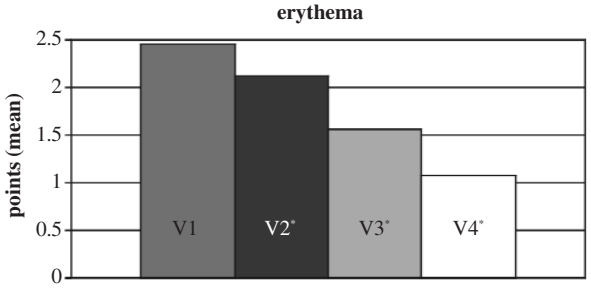
Results

Thirty-nine of forty enrolled subjects completed the study. One female subject, aged 48 years, who suffered from seborrheic dermatitis, was withdrawn from the trial because of contact dermatitis which occurred after 2 days of treatment. Improvement in skin appearance characterized by the total remission of skin lesions (category I) was observed in 10% of subjects according to the doctors'

Table 2. Evaluation of appearance of erythema at baseline, and after 7, 14 and 21 days of treatment

Points	Study group [n=39]			
	V1 [n]	V2 [n]	V3 [n]	V4 [n]
0	–	–	1	9
1	3	12	25	21
2	21	15	5	7
3	9	7	6	–
4	6	5	2	2
Total	39	39	39	39

V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days; 0 points – no symptoms, 1 point – mild, 2 points – moderate, 3 points – severe, 4 points – very severe



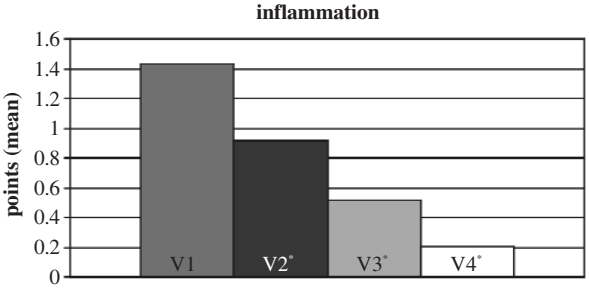
**significant difference from baseline; V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days*

Figure 2. Changes in skin appearance measured by the erythema severity score during the study period

Table 3. Evaluation of redness and inflammatory conditions in inflammation at baseline, and after 7, 14 and 21 days of treatment

Points	Study group [n=39]			
	V1 [n]	V2 [n]	V3 [n]	V4 [n]
0	3	10	21	33
1	17	22	16	4
2	18	7	2	2
3	1	–	–	–
4	–	–	–	–
Total	39	39	39	39

V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days; 0 points – no symptoms, 1 point – mild, 2 points – moderate, 3 points – severe, 4 points – very severe



**significant difference from baseline; V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days*

Figure 3. Changes in appearance of skin affected by inflammation measured by the severity score during the study period

opinion and in 15% of cases according to the subjects' self assessment (Figure 1); improvement from definite to slight (II–III) was observed in 87% and 74% according to doctors and self-assessment, respectively; and finally no effect (category IV) was seen in 3% and 10%, respectively (table 1). No exacerbation of clinical status as compared to the baseline was reported by either subjects or doctors.

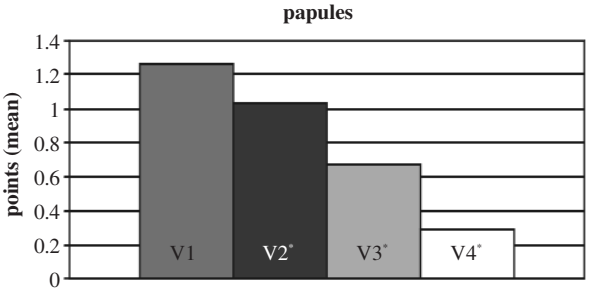
Detailed results of the study are presented in tables 2-8. Tables 2-6 provide the results for selected skin lesions (Figures 2-6, respectively). Tables 7 and 8 provide the scores for pruritus and burning sensations recorded during the study period (Figures 7 and 8, respectively). The clinical improvement as measured by the scores for erythema, inflammation, papules, pustules, teleangiectasia, pruritus and burning sensations as well as for the severity of global dermatological status were statistically significant. A significant improvement in skin appearance measured by reduction of erythema, inflammation, papules and pruritus was recorded on day 7 (Figures 2-4 and 7, respectively). A significant reduction in teleangiectasia (Figure 6) and burning (Figure 8) scores was noted on day 14, and a significant reduction in pustules was recorded on day 21 (Figure 5). There was no significant difference between subjects' and doctors' opinions regarding the efficacy of the study product.

Possible adverse events and/or concomitant remedies were recorded throughout the study period. One study subject noted above, a female with seborrheic dermatitis, was excluded at visit 1 (day 7) because of severe erythema and oedema of the face which was restricted to the area of product application and occurred on day 2 of treatment. This condition was diagnosed as contact dermatitis. The signs and symptoms of contact dermatitis diminished after discontinuation of the study and administration of antihistamines. In 7 subjects (3 with seborrheic dermatitis, 2 with rosacea and

Table 4. Evaluation of skin appearance by the papule count at baseline, and after 7, 14 and 21 days of treatment

Points	Study group [n=39]			
	V1 [n]	V2 [n]	V3 [n]	V4 [n]
0	6	9	16	28
1	20	21	20	11
2	10	8	3	–
3	3	1	–	–
4	–	–	–	–
Total	39	39	39	39

V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days; 0 points – no symptoms, 1 point – mild, 2 points – moderate, 3 points – severe, 4 points – very severe



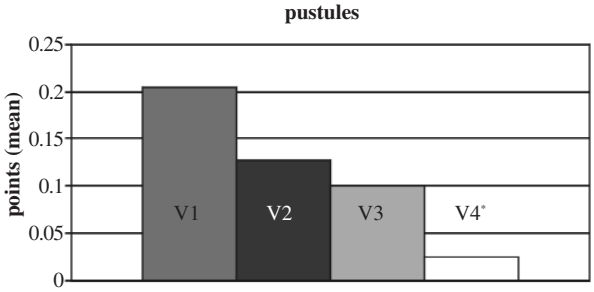
**significant difference from baseline; V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days*

Figure 4. Changes in skin appearance measured by the papules severity score during the study period

Table 5. Evaluation of skin appearance by the pustule count at baseline, and after 7, 14 and 21 days of treatment

Points	Study group [n=39]			
	V1 [n]	V2 [n]	V3 [n]	V4 [n]
0	33	35	35	38
1	4	3	4	1
2	2	1	–	–
3	–	–	–	–
4	–	–	–	–
Total	39	39	39	39

V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days; 0 points – no symptoms, 1 point – mild, 2 points – moderate, 3 points – severe, 4 points – very severe



**significant difference from baseline; V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days*

Figure 5. Changes in skin measured by the pustules severity score during the study period

2 with perioral dermatitis) exacerbation of skin burning and pruritus together with dryness and tingling was noted. Those symptoms occurred at different time points of the study but were transient and disappeared after 7-14 days of further product application. In 3 cases, concomitant moisturisation was necessary together with application of 1,4-cyclohexanediol gel. Irrespective of these minor adverse events, a definite improvement in final skin condition was reported in all of these cases based on both doctor's and subjects' evaluation. Six of these subjects rated the overall effect of the product as a definite improvement, and one scored it as a slight improvement.

Discussion

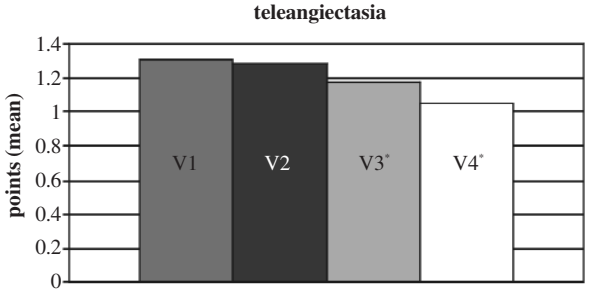
A cis/trans mixture of 1,4-cyclohexanediol is a dihydroxylic cyclic alcohol with chemical formula $C_6H_{12}O_2$, and molecular weight of 116. It is also called chinit in organic chemistry textbooks [4]. It is a metabolite of menthol and cyclohexane (Figure 9). 1,4-cyclohexanediol is a urinary biomarker of exposure to cyclohexane. Possible sources of cyclohexane in humans are intravenous dextrose, parenteral feeding solution, some parenteral cephalosporins and inhalation of vapour in the workplace (for example, in shoe and leather factories) [5-8]. Menthol is a constituent of peppermint and cornmint, which has been used as an ingredient in various pharmaceuticals and cosmetics for many years. It has a characteristic smell and taste and causes a cooling sensation and a reduction in itching after topical application [9,10].

The safety of 1,4-cyclohexanediol has been extensively evaluated in previous studies (Cinna Health Products, data not published). Those studies were designed to comply with international standards for chemical substances. No toxic effect was observed at doses of up to 5000 mg/kg in the standard LD50 test. Neither cis nor trans 1,4-cyclohexanediols have genotoxic

Table 6. Evaluation of skin appearance by intensity of teleangiectasia at baseline, and after 7, 14 and 21 days of treatment

Points	Study group [n=39]			
	V1 [n]	V2 [n]	V3 [n]	V4 [n]
0	10	10	10	12
1	14	15	17	18
2	10	9	9	7
3	3	3	1	–
4	2	2	2	2
Total	39	39	39	39

V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days; 0 points – no symptoms, 1 point – mild, 2 points – moderate, 3 points – severe, 4 points – very severe



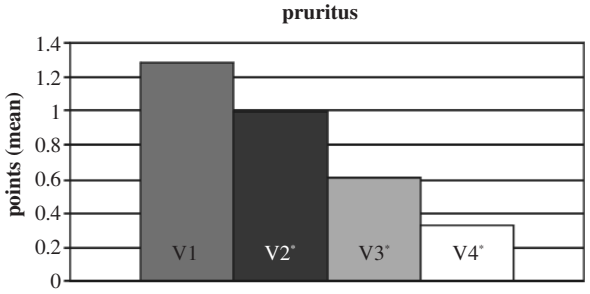
**significant difference from baseline; V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days*

Figure 6. Changes in skin appearance measured by the teleangiectasia severity score during the study period

Table 7. Evaluation of skin by intensity of pruritus at baseline, and after 7, 14 and 21 days of treatment

Points	Study group [n=39]			
	V1 [n]	V2 [n]	V3 [n]	V4 [n]
0	7	10	19	28
1	15	20	17	10
2	16	8	2	–
3	1	1	1	1
Total	39	39	39	39

V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days; 0 points – no symptoms, 1 point – mild, 2 points – moderate, 3 points – severe, 4 points – very severe



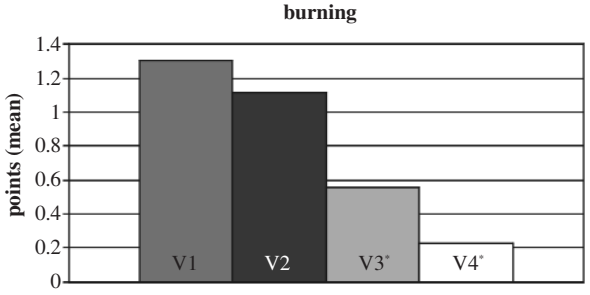
**significant difference from baseline; V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days*

Figure 7. Changes in skin measured by the pruritus severity score during the study period

Table 8. Evaluation of skin by intensity of burning sensations at baseline, and after 7, 14 and 21 days of treatment

Points	Study group [n=39]			
	V1 [n]	V2 [n]	V3 [n]	V4 [n]
0	10	12	23	30
1	14	15	11	9
2	8	7	4	–
3	7	5	1	–
Total	39	39	39	39

V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days; 0 points – no symptoms, 1 point – mild, 2 points – moderate, 3 points – severe, 4 points – very severe



**significant difference from baseline; V1 – baseline, V2 – visit 2 after 7 days, V3 – visit 3 after 14 days, V4 – visit 4 after 21 days*

Figure 8. Changes in skin appearance measured by the burning sensations severity score during the study period

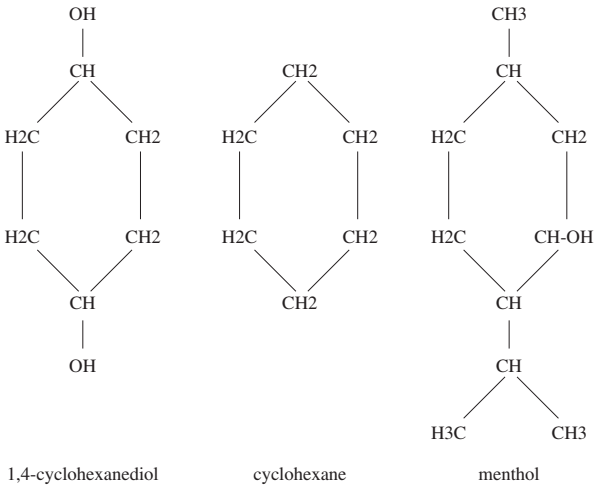


Figure 9. Chemical structure of 1,4-cyclohexanediol, cyclohexane and menthol

activity in the bacterial mutation test or in the chromosomal aberration test with human cell lines. The photostability of 1,4-cyclohexanediol was established after exposure to a xenon beam source (75 W/m^2). Its chemical stability was established by the lack of any significant reduction in the recovered concentration of 1,4-cyclohexanediol exposed to thermal stress, and acid or base hydrolysis conditions. A loss in recovered analyte concentration approaching 50% was observed under conditions of oxidative stress produced by hydrogen peroxide at 80°C. Collectively, these results indicate the safety and high chemical stability of 1,4-cyclohexanediol.

No studies with animals have been performed using a cosmetic formula containing the 1,4-cyclohexanediol gel. No bacteria or fungi were detected in the 1,4-cyclohexanediol gel after 3 weeks of incubation in bacterial growth medium. No microorganisms were detected in microbiological evaluations which tested the product for the presence of *Pseudomonas*

aeruginosa, *Staphylococcus aureus* or *Candida albicans*. In addition, 1,4-cyclohexanediol inhibited in a dose-dependent fashion the growth of several bacteria, which included: *Escherichia coli*, *Citrobacterium braaki* (gram-), *Bacillus subtilis* (gram+). No allergic or other adverse effect was observed in contact studies done on subjects with a history of allergy (skin condition was examined after 48, 72 and 96 hrs). A previous large, prior double blind study (HTR No 98-100675-70; 88 subjects enrolled and 74 completed the entire study) conducted to evaluate the efficacy of the test substance showed that 1,4-cyclohexanediol is an effective cosmetic in improving skin condition and reducing skin redness (manuscript in preparation).

Results of the present study, performed on a group of 40 subjects affected by seborrheic dermatitis, rosacea, perioral dermatitis and face dermatitis (39 completed all stages of the study), revealed a statistically significant clinical improvement related to erythema, inflammation, papules, pustules or teleangiectasia. A statistically significant improvement in skin health based on reduction of pruritus and burning sensations was also observed. The clinical improvement in terms of erythema, inflammation, papules and pruritus was noted as early as day 7. The improvement in relation to pustules, teleangiectasia and burning sensations was observed from days 14 to 21. Both doctors and subjects evaluated the study product as being a highly effective cosmetic for sensitive, erythematous skin.

The adverse events documented throughout the study period included one female subject who developed contact dermatitis and 7 subjects reporting exacerbation of burning sensations, pruritus with dryness and tingling. Those symptoms were transient and disappeared after a few successive applications of the gel. In 3 cases, a moisturiser was used together with 1,4-cyclohexanediol gel application. Irrespective of those minor adverse events, in all cases a definite improvement in skin condition was observed. In addition to the improvement in skin appearance, the 1,4-cyclohexanediol gel also significantly reduced pruritus and burning skin sensations.

The present study indicates that 1,4-cyclohexanediol gel, a new skin care gel, has a beneficial effect on the condition of sensitive skin in subjects affected by rosacea, seborrheic dermatitis or perioral dermatitis. The beneficial effects of 1,4-cyclohexanediol gel on the skin requires continued, daily application.

In conclusion, 1,4-cyclohexanediol gel is a safe and effective cosmetic product for routine application to sensitive skin with erythematous conditions.

*trade name – Noredol™ Gel, Cinna Health Products, MRC, Cincinnati, Ohio, USA

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