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Study No.: D2250298	
Title: An irritation patch test of topical formulations containing aciclovir	
Rationale: In order to improve the stability of acyclovir 5% cream, the formulation was modified. The purpose of this study was to evaluate the irritancy of the acyclovir 5% cream test formulations compared to the reference marketed product.	
Phase: I	
Study Period: 25 February 2004 – 5 March 2004	
Study Design: Single center, randomized, single blind, within subject study in healthy volunteers	
Centres: Single center, Scotland	
Indication: Cold sores (herpes simplex virus type 1, HSV-1)	
Treatment: A marketed aciclovir 5% cream (reference control), 4 test formulations of aciclovir 5% cream, and saline (negative control) on patch strips for 4 on-treatment days, where Formulation 1 contained cetomacrogol; Formulation 2 contained arlacel 165 + 0.5% SLS; Formulation 3 contained arlacel 165 + 0.75% SLS; and Formulation 4 contained sodium lauryl sulphate.	
Objectives: To assess the irritation potential of four acyclovir cream test formulations compared with a marketed formulation when applied to the skin under occlusion for 96 hours.	
Primary Outcome/Efficacy Variable: Irritation score (sum of erythema and dryness scores) averaged over the entire study period (Days 2-5)	
Secondary Outcome/Efficacy Variable(s): Erythema and dryness scores averaged over the entire study period (Days 2-5), daily irritation, erythema, and dryness scores	
Statistical Methods: The irritation, erythema and dryness scores were ranked from smallest to largest within each subject. The ranked values were then separately subjected to a two-way non-parametric analysis of variance based upon Friedman rank sums with adjustment being made for tied values. Where the two-way analysis of variance revealed a statistically significant study product(s) effect at a 5% significance level, then pairwise comparisons of interest were performed using a non-parametric procedure based on Friedman rank sums. All tests were two-tailed and in order to attain an overall 5% significance level, a Bonferroni adjustment for multiple comparisons was applied (i.e. $p < 0.006$ for each pairwise comparison).	
A negative median difference between an acyclovir 5% cream test formulation and a reference (marketed cream or saline) favored the test formulation.	
Study Population: Healthy volunteers aged 18 to 65 years	
Number of Subjects Screened:	33
Planned, N	Approx 30
Randomised, N	28 randomized
Completed, n (%)	26
Total Number Subjects Withdrawn, N (%)	2
Withdrawn due to Adverse Events n (%)	0
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for other reasons n (%)	2
Demographics	
N (ITT)	27
Females: Males	13:14
Mean Age, years (SD)	45.6 (11.8)
White, n (%)	26 (96.3)

Primary Efficacy Results: Irritation Score				
	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Irritation Score				
Median difference (test - marketed formulations)	-0.38	0.00	0.25	0.75
95% Confidence Interval	-1.13, 0.13	-0.38, 0.25	-0.13, 0.75	0.25, 1.25
p-value	0.35	0.76	0.018	<0.001
Median difference (test - saline formulations)	1.13	1.50	2.00	2.38
95% Confidence Interval	0.63, 1.63	1.00, 2.38	1.25, 2.75	1.75, 3.13
p-value	<0.001	<0.001	<0.001	<0.001
Secondary Outcome Variable(s): Erythema and dryness scores				
	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Erythema Score				
Median difference (test - marketed formulations)	-0.38	0.00	0.25	0.75
95% Confidence Interval	-1.13, 0.13	-0.38, 0.25	-0.25, 0.75	0.25, 1.25
Median difference (test - saline formulations)	1.13	1.50	2.00	2.50
95% Confidence Interval	0.75, 1.63	1.00, 2.38	1.25, 2.63	1.75, 3.13
Dryness Score				
Median difference (test - marketed formulations)	0.00	0.00	0.00	0.00
95% Confidence Interval	0.00, 0.00	0.00, 0.00	0.00, 0.13	0.00, 0.00
Median difference (test - saline formulations)	0.00	0.00	0.00	0.00
95% Confidence Interval	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.00, 0.00
Safety Results: AEs collected from time of first dosing, up to 28 days after last dose (or ½ life of product, whichever is longer)				
				N=28
Most Frequent Adverse Events – On-Therapy				
Subjects with any AE(s), n(%)				2 (7.1)
Runny nose				1 (3.6)
Facial injury				1 (3.6)
Serious Adverse Events - On-Therapy				
				N=28
Subjects with non-fatal SAEs, n (%)				0
Subjects with fatal SAEs, n (%)				0
Conclusion: Each of the test formulations was well tolerated.				
The data from this study indicate Formulations 1, 2, and 3 would be suitable to develop further.				
Publications: None				