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1. TITLE PAGE

CLINICAL STUDY REPORT

**REDUCTION OF THE GINGIVAL INFLAMMATION BY "V0109 DI".
RANDOMISED, PARALLEL GROUPS, DOUBLE BLIND STUDY, V0109 DI
VERSUS PLACEBO, IN PATIENTS PRESENTING GINGIVITIS**

Investigational product: V0109 DI / Gingival paste

Study Design: Multicentre, randomised, international, double blind phase III_b study, on two parallel groups, placebo versus V0109 DI.

Protocol number: V00109 DI 301

EudraCT number **2008-000990-39**

Phase of development: Phase III_b

Date of first enrolment: August 27th, 2008

Date of last completed: December 12th, 2008

Co-ordinator: Dr Liga KRONINA, Dental Clinic Akribija
Skolas Street 9 – 1, Riga, LV - 1010

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Date of report: May 26, 2011

Study performed in compliance with Good Clinical Practice.

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2. SYNOPSIS

Name of Company: Pierre Fabre Médicament		Individual Study Table Referring to Module 5 of the Dossier Vol.:Page:	(For National Authority Use Only)
Name of active substance: Enoxolone 1 g for 100 g			
Title of study:	Reduction of the gingival inflammation by "V0109 DI". Randomised, parallel groups, double blind study, V0109 DI versus placebo, in patients presenting gingivitis.		
Investigator-coordinating:	Dr. Liga KRONINA		
Study centres:	Dentists selected for their expertise in gingivitis. 3 centres in Estonia and 1 centre in Latvia		
Publication (reference):	NA		
Studied period:	date of first enrolment: August 27 th , 2008 date of last completed: December 12 th , 2008	Phase of development: Phase III _b	
Objectives:	Primary: To assess the efficacy of V0109 DI in reducing gingival inflammation in patients with gingivitis. Secondary: <ul style="list-style-type: none"> - To assess the effect of V0109 DI on gingival bleeding, - To assess the activity of V0109 DI on dental plaque, - To assess the local and general tolerance. 		
Methodology:	Multicentre, randomised, international, double blind phase III _b study, on two parallel groups, placebo versus V0109 DI.		
Number of patients (planned and analysed):	54 patients were planned, divided into 27 patients by treatment group. 82 patients were screened and 61 randomised (30 in the placebo group and 31 in the V0109 DI group)		
Diagnosis and main criteria for inclusion:	were eligible patients (male or female) who met the following criteria: <ul style="list-style-type: none"> - age between 18 and 45 years inclusive, - be non smoker, - have a minimum of 20 natural teeth (excluding wisdom teeth) and good dental health (except gingivitis), - have a toothbrush and toothpaste, - have gingivitis (Gingival Index $\geq 1,5$). 		
Test product:	V0109 DI: Gingival paste containing Enoxolone 1% Dose: 3 times daily after each meal. Mode of administration: Tooth brushing followed by a direct gingival massage during one minute. A half finger top joint of gingival paste was used for tooth brushing, followed by another amount of a half finger top joint of gingival paste to perform gingival massage during 1 minute. Gingival paste was then removed by a mouthwash using water. Batch number: SB0669		
Reference therapy:	Placebo: Gingival paste, Dose: 3 times daily after each meal. Mode of administration: Tooth brushing followed by a direct gingival massage during one minute. A half finger top joint of gingival paste was used for tooth brushing, followed by another amount of a half finger top joint of gingival paste to perform gingival massage during 1 minute. Gingival paste was then removed by a mouthwash using water. Batch number: SB0666 SB0691		
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Name of Company: Pierre Fabre Médicament	Individual Study Table	(For National Authority Use Only)
	Referring to Module 5 of the Dossier	
Name of active substance: Enoxolone 1 g for 100 g	Vol.:Page:	
Duration of treatment:	14 days.	
Criteria for evaluation:	Efficacy: Primary criterion: The main criterion was the evolution of the Loe and Silness Gingival Index (GI) during the study: mean change between D0 and D14 calculated on 6 sites (3 vestibular and 3 palatin) around 6 target teeth, excluding wisdom teeth. Secondary criteria: <ul style="list-style-type: none"> - the percentage of bleeding sites on probing (or spontaneously) was assessed on 6 sites around 6 target teeth, excluding wisdom teeth. The quotation at each site was present / absent, - plaque accumulation was assessed on both facial and lingual surfaces on 6 target teeth, excluding wisdom teeth, according to the Turesky modification of the Quigley and Hein Plaque Index (PI), Safety: <ul style="list-style-type: none"> - local tolerance: aspect of the mouth mucosa, - general tolerance (adverse events), 	
Statistical methods:	<ul style="list-style-type: none"> - Efficacy: non-parametric analysis of covariance, - Safety: descriptive analysis. 	
Summary - Conclusions: Efficacy results The primary analysis concerned the evolution of Gingival Index (GI). After two weeks of treatments (i.e. from V2 to V4) the mean change of GI was -0.49 ± 0.39 in the placebo group and -0.51 ± 0.41 in the V0109DI group ($p = 0.9731$). There was insufficient difference on Bleeding on Probing. After two weeks of treatment (i.e. from V2 to V4), we could only notice a trend to a better improvement of bleeding reduction with V0109 DI (-32.13 ± 21.60) than placebo (-28.52 ± 22.43) ($p=0.1637$). The mean change of Plaque Index (PI) from V2 to V4 was -0.41 ± 0.41 with placebo and -0.41 ± 0.55 with V0109DI ($p=0.3289$). Safety results A total of 61 patients used the study treatment at least once. TEAEs occurred in a total of 15 patients (6/30 in placebo group and 9/31 in V0109DI group). The relationship to study treatment was not excluded in 13 patients (6 in placebo group and 7 in V0109DI group). It concerned dryness of the mouth, gingival pain, glossodynia, lip pain, sensitivity of teeth, oral paresthesia and oral herpes. None of these potentially related TEAE led to an interruption of the treatment. Adverse event led to definitive discontinuation of the treatment in one patient (1/31 in V0109DI group). The relationship with the study product was excluded by the investigator. Moreover, this adverse event was previously reported by the investigator in the patient's medical history. Other observations related to safety were reported and categorized as local tolerance (Erythema, Oedema and Ulceration). Their frequencies were quite similar in each category for both groups. The intensity of symptoms was mostly mild or moderate. No serious and no unexpected adverse event was observed during the course of the study. Conclusion This study evaluated the effects of 14-day administration/application of V0109DI in patients suffering from gingivitis. In the experimental conditions planned by the protocol, it was not possible to show differences on efficacy parameters between V0109DI and placebo. The tested product V0109DI was as well tolerated as the placebo.		
Date of report: May 26, 2011		
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