Pierre Fabre Médicament
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CLINICAL STUDY REPORT

VOLUME 1/6

V00132 CR 401
Efficacy study of CIRKALM® cream versus placebo in the treatment of anal pain

Investigational product: (CIRKALM® cream)

Study Design: National, multicentre, randomised, double-blind, placebo-controlled, phase IV study

Protocol number: V00132 CR 401

Phase of development: IV

Study initiation date: 28 October 2008

Study completion date: 10 December 2009

Coordinator and Principal Investigator:
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Date of report: Final version of 15 March 2011

The study was performed in compliance with Good Clinical Practice including the archiving of essential documents.

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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 finished product: Cirkalm® cream		
Name of active substance: *Ruscus aculeatus* (butcher's broom), Hesperidin methyl chalcone, Heparin sodium		

Title of study:	**Efficacy study of CIRKALM® cream versus placebo in the treatment of anal pain**	
Investigators:	Coordinator: Dr Laurent Abramowitz, Unité de Proctologie médico-chirurgicale, Hôpital Bichat-Claude-Bernard, 46, rue Henri-Huchard, 75877 Paris Cedex 18. Investigators were general practitioners and gastroenterologists.	
Study centres:	Twenty-seven centres located in France.	
Publication (reference):	NA	
Studied period: **(date of first enrolment)** **(date of last completed)**	Date of first enrolment: 28 October 2008 Date of last completed: 10 December 2009	**Phase of development:** IV
Objectives:	**Primary:** The primary objective was to assess the change in pain intensity during the first fourteen days of treatment (average daily pain experienced). **Secondary:** The secondary objectives of this trial were the following: • To assess changes in anal pain intensity between Day 1 and Day 42 (most intense pain, pain experienced during defecation). • To assess the fissure healing at 6 weeks. • To assess the need for paracetamol treatment. • To assess changes in bleeding frequency between Day 1 and Day 42. • To study the change in anal pruritus between Day 1 and Day 42. • To describe overall improvement according to the patient. • To describe the treatment compliance. • To assess local and systemic clinical tolerance.	
Methodology:	This was a national, multicentre, prospective, randomised, double-blind, placebo-controlled study. The study included: • 3 visits: Day 1 (Inclusion/randomization visit), Day 14 (Follow-up visit) and Day 42 (Final visit). • A patient daily self-evaluation from Day 1 to Day 41.	
Number of patients (planned and analysed):	Number of patients planned: 132. Number of patients analysed: 126.	
Diagnosis and main criteria for inclusion:	The study included adult male and female patients presenting with anal fissure symptoms as defined by anal pain that can last from a few minutes to a few hours associated with presence of blood on the toilet paper, and with average anal pain score: > 50 mm as self-assessed using a 100-mm Visual Analogue Scale (VAS) scale. The main exclusion criteria were: (i) Patient with thrombosis, anal margin abscess or suppuration, inflammatory, dermatogical, neoplastic, infectious or parasitological diseases of anorectal region or any other anorectal pathology requiring different	

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	management than those planned in the protocol. (ii) Patient requiring hospitalisation and/or surgical treatment. (iii) Patient already receiving a medical treatment for anal fissure.
Test product, Dose, Mode of administration, Batch number:	CIRKALM® cream. Active substances (qs 100 g): 2.52 g *Ruscus aculeatus* - butcher's broom (dry hydroalcoholic extract containing 50% total sterolic heterosides), 1.00 g hesperidin methyl chalcone, and 62 500 IU heparin sodium. Twice daily local application at the site of the anal fissure, as possible after evacuation. Batch number SB0560 (expiry date March 2010)
Duration of treatment:	42 days
Reference therapy, Dose, Mode of administration, Batch number:	Placebo cream, twice daily local application at the site of the anal fissure, as possible after evacuation. Batch number SB0663 (expiry date January 2010)
Criteria for evaluation:	**Primary efficacy criterion:** • Changes in average pain intensity experienced over the first fourteen days of treatment. **Secondary efficacy criteria:** • Changes in the level of the most severe pain experienced between Day 1 and Day 42, • Change of level of pain during defecation between Day 1 and Day 42, • Use of paracetamol, • Fissure healing at 6 weeks, • Changes in anal bleeding frequency between Day 1 and Day 42, • Changes in anal pruritus between Day 1 and Day 42, • General improvement, • Compliance with treatment. **Safety:** Rate of adverse events.
Statistical methods:	**Analysed data set:** • Full analysis set (FAS): all randomised patients having taken at least one dose of study drug (placebo or Cirkalm®). Patients were analysed according to the intent-to-treat principle. • Per Protocol (PP) set: all randomised patients without any major protocol deviation. • Safety Set: all randomised patients having taken at least one dose of study drug (placebo or Cirkalm®). Patients were analysed according to the treatment actually taken. **Statistical Analysis:** • Analyses were performed on an intent-to-treat basis and per protocol. • All tests were two-tailed and the statistical significance threshold was 0.05. Standard descriptive statistics were performed using all available data. Group comparisons were performed using the Student's t-test, the Wilcoxon's rank sum test, the Pearson's Chi-square, or the Fisher's exact test, as appropriate. • A repeated measure ANOVA was performed to assess the effect of time and treatment group on the changes in average pain intensity, most intense pain,

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pain during defecation and anal pruritus.

- A sensitivity analysis using the last-observation-carried forward (LOCF) method was performed to determine robustness of the conclusions.

Summary - Conclusions:

Efficacy results

Data sets analysed

- The FAS consisted of all the 126 patients included in the study: 61 patients in the Cirkalm® group and 65 patients in the placebo group.
- The PP set consisted of 91 patients. The proportion of patients with at least one protocol deviation was similar between the two groups: 18 (29.5%) patients in the Cirkalm® group and 17 (26.2%) patients in the Placebo group (p=0.674). The main protocol deviations were missing data for the evaluation of the primary efficacy criterion and the delays between treatment periods not respected.
- The Safety Set consisted of all the 126 patients included in the study. All patients took the treatment to which they were allocated.

The following results are described in the FAS.

Patient baseline characteristics

Patient's baseline characteristics were similar in the two groups. Overall, the majority of patients were female (56.3%) with a mean age of 47.0 ± 14.9 years. The clinical features of anal fissure were similar in the Cirkalm® group and in the placebo group. Anal fissure was superficial in the vast majority of patients. More than half of the patients (54.8%) had an anterior fissure while the fissure was posterior in 48 (38.1%) patients. Hypertonia of the anal sphincter was reported in half of the patients (50.0%). The severity of anal pain related to anal fissure did not differ between the two groups. The average pain intensity assessed by using a 100-mm VAS was 64.2 ± 19.2 mm. The mean VAS score did not differ between the two groups. The mean VAS scores assessing the most intense pain felt and defecation pain were 71.2 ± 21.1 mm and 67.5 ± 23.5 mm, respectively, without significant difference between groups.

Primary efficacy criterion

Overall, the average pain intensity decreased during the treatment period, including the first fourteen days, in the Cirkalm® group and in the placebo group. The pattern of decrease was similar in the two groups. Consistently, the analysis of the effect of time and treatment group using ANOVA showed that time impacted the change in average pain intensity between Day 12 and Day 16 ($p< 0.001$) whereas the treatment group had no significant effect (p=0.307). Similar results were observed for changes from baseline of average pain intensity on Day 14 and Day 41.

Secondary efficacy criteria

- Changes of most intense pain felt, pain during defecation and anal pruritus during the treatment between Day 1 and Day 41:

  The most intense pain felt, pain during defecation and anal pruritus decreased between Day 1 and Day 41 with a similar pattern of decrease in the two groups. The analyses of the effect of time and treatment group on the change of most intense pain felt and of pain during defecation between Day 1 and Day 41 show that both time and treatment had a significant effect. However, there was no interaction between time and treatment. Similar results were observed for the change of anal pruritus.
- Use of paracetamol:

  One third of patients (34.7%) used paracetamol at least once during the study. The proportion of patients who used paracetamol did not differ between the Cirkalm® and the placebo group (p= 0.475).
- Fissure healing at Day 42:

  The rates of fissure healing did not differ between the two groups: 32 (52.5%) patients in the Cirkalm® group and 34 (52.3%) patients in the placebo group (p=0.986).
- Change of anal bleeding frequency between Day 1 and Day 42:

  The frequency of anal bleeding decreased in both groups between Day 1 and Day 42. The presence of anal bleeding did not differ for each day between the Cirkalm® group and the placebo group.
- General improvement:

  The vast majority of patients (75.6%) perceived the treatment as "very satisfying" or "satisfying". The feeling of

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general improvement did not differ between the Cirkalm® group and the placebo group.

- Compliance with treatment:
  In the FAS, approximately one third of patients (31.4%) was 100% compliant, one third (30.5%) was at least 80% compliant and one third (38.1%) was less than 80% compliant. The compliance to the treatment did not differ between the two groups.

The results obtained in the PP set were similar to those obtained in the FAS.

Safety results

No deaths or serious adverse events occurred during the study.

- 25 (19.8%) patients in the Safety Set reported at least one adverse event (AE) during the study. The proportion of patients with at least one AE was similar between the two groups: 12 (19.7%) patients in the Cirkalm® group and 13 (20.0%) in the placebo group (p=0.963).
- The proportion of patients with at least one treatment emergent adverse events was 16.5%: 10 (16.9%) patients in the Cirkalm® group and 10 (16.1%) in the placebo group (p=0.903).
- A total of 34 AEs was reported during the study: 18 AEs in the Cirkalm® group and 16 AEs in the placebo group.
- The vast majority (85%) of the AEs were mild or moderate in intensity. Severe AEs were only reported in the placebo group.

Conclusion:

This randomized, controlled study did not show the efficacy of Cirkalm® cream in the treatment of anal pain compared to placebo. Consequently, the use of Cirkalm® cream in the treatment of anal fissure is not supported by the results of this study. The use of Cirkalm® cream raised no safety concerns.

Date of report: 15 March 2011