Pierre Fabre Médicament
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CLINICAL STUDY REPORT

Double-blind, placebo-controlled study of the efficacy and safety of Bicirkan® on functional venous symptoms experienced (C0s to C3s) by obese female patients

Investigational product: L00085 / Bicirkan®

Protocol number: L000 85 CP 403

EudraCT number: 2007-000652-14

Phase of development: Phase IV

Date of first enrolment: June 2007

Date of last completed: December 2007

Co-ordinator: Prof. François-André ALLAERT
24 bvd Jeanne d'Arc 21000 Dijon-France

Sponsor Representative(s) for study report:

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Date of report: 13 April 2011

Study performed in compliance with Good Clinical Practice.

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Summary

Sponsor:	Pierre Fabre Médicament	
Medicinal product:	Bicirkan®	
Active ingredient:	Dry ruscus extract 80.00 mg - Hesperidin methyl chalcone 200.00 mg Ascorbic acid 400.00 mg	
Study title	Double-blind, placebo-controlled study of the efficacy and safety of Bicirkan® on functional venous symptoms experienced (C0s to C3s) by obese female patients	
Coordinator	Prof. François-André Allaert 24 bvd Jeanne d'Arc 21000 Dijon-france	
Investigation centre	Dr Jean-Patrick Benigni, Dr Christian Hugue, Dr Jean-Marc Renaudin, Prof. Pierre Escourou	
Study period	June 2007 - December 2007	Clinical phase: IV
Objectives	**Primary objective**: Evaluate the efficacy of Bicirkan® on the painful discomfort experienced by obese female patients with stage C0s to C3s venous insufficiency. **Secondary objectives**: Evaluate the efficacy of Bicirkan® on other symptoms induced by venous disease in obese female patients. Evaluate the safety of Bicirkan® in obese female patients.	
Methodology	Multicentre, randomised, controlled parallel group, double-blind placebo-controlled study.	
Number of female patients	30 female patients per study arm were required, 52 were included :24 in the placebo group, 28 in the Bicirkan group.	
Patient screening criteria	**Inclusion criteria**: Women: - over the age of 18 having given written, informed consent, with French social security cover or equivalent cover, not likely to be pregnant or to fall pregnant during the study - and with obesity as defined by a BMI of over 30, and stage C0s to C3s venous disease, characterised by painful discomfort evaluated at over 40 mm and under 70 mm on a 0 to 100 mm visual analogue scale. **Exclusion criteria** Women: - with severe medical or psychiatric condition/disease, considered by the investigator to be dangerous for the volunteer or incompatible with the trial procedure, known allergy to the product or excipients, urinary disorders i.e. oxalic, cysteine and uro- lithiasis, G6PD deficiency, trophic disorders, static foot disorders, gastrocnemius vein diameter greater than 6mm; - currently using phlebotonic or contention treatment, or having been treated by one of these methods in the 4 previous weeks.	
Test Product: **Dose:** **Method of administration:**	Bicirkan® 4 tablets per day: 2 tablets at breakfast and 2 tablets at lunch Oral	
Duration of treatment	3 weeks	
Reference treatment: **Dose:** **Method of administration:**	Placebo 4 tablets per day: 2 tablets at breakfast and 2 tablets at lunch Oral	

Primary endpoint	Clinically-significant reduction in painful discomfort after three weeks (D21) full treatment, defined by a reduction of at least 30% in the pain intensity measured on a VAS compared to the value at inclusion.
Secondary endpoints	Change at D7, D14, and D21 in the intensity of the functional symptoms induced by venous disease: painful discomfort, heavy legs, paresthesia, pruritus, cramps; Change at D7, D14, and D21 in the time of occurrence and of the acme period of the symptoms induced by venous disease (painful discomfort, heavy legs, paresthesia, pruritus, cramps); Description of clinical safety: collection of adverse events and their date of occurrence.
Statistical methods	**Analysis Sets** The ITT set comprised all patients having received at least one study treatment and having a pain assessment evaluation at inclusion visit The PP set comprised all patients without any major deviation The safety set comprised all patients having received at least one study treatment **Primary endpoint** The primary endpoint was the change in painful discomfort measured by the female patient in the medical practices at the first and second visit, on an analogue scale. The percentage of female patients in whom the painful discomfort was reduced by at least 30% at the V2 visit compared to the V1 visit was compared at the end of the study between the two groups, by a CHI square test or its non-parametric equivalent if required. The statistical significance threshold was set at 5%. **Secondary endpoints** The secondary endpoints were all other functional signs, which was compared using the same technique. The percentage and nature of the adverse events was compared using Chi square tests. The kinetics of change in the primary endpoint and secondary endpoints was also compared via self-questionnaires, by analysis of variance on repeated series, as well as the time to appearance of venous symptoms over the day.
Results	52 females were included:24 in the placebo group, 28 in the Bicirkan group. The ITT analysis covered 47 female patients, 22 in the Bicirkan group and 22 in the Placebo group. Demographic characteristics, venous risk factors, functional signs (painful discomfort, paresthesia, pruritus, cramps and swelling) and physical signs (CEAP) were comparable at inclusion. The results for the primary endpoint, represented by the percentage of female patients in whom painful discomfort is reduced by at least 30% at the V2 visit compared to the V1 visit are given in the table below, and do not show any significant difference between the two Bicirkan and Placebo groups.

Change in painful discomfort		Placebo		Bicirkan		Total		Chi² *Fisher*
		N	%	N	%	N	%	
D0-D7	Less than 30%	11	57.9	17	70.8	28	65.1	NS
	30% and over	8	42.1	7	29.2	15	34.9	
	Total	19	100.0	24	100.0	43	100.0	
D0-D14	Less than 30%	7	36.8	10	41.7	17	39.5	NS
	30% and over	12	63.2	14	58.3	26	60.5	
	Total	19	100.0	24	100.0	43	100.0	
D0-D21	Less than 30%	7	36.8	8	33.3	15	34.9	NS
	30% and over	12	63.2	16	66.7	28	65.1	
	Total	19	100.0	24	100.0	43	100.0	

	The same applied when we compared the means for the painful discomfort at the various visits, to the values observed at inclusion. **D0** / AVE ± Sd: Placebo 56.8 ± 13.4; Bicirkan 52.3 ± 13.0; Total 54.4 ± 13.2; Anova NS **D7** / AVE ± Sd: Placebo 34.7 ± 28.6; Bicirkan 41.0 ± 22.3; Total 38.2 ± 25.2; Anova NS **D14** / AVE ± Sd: Placebo 28.0 ± 28.5; Bicirkan 24.9 ± 27.0; Total 26.3 ± 27.4; Anova NS **D21** / AVE ± Sd: Placebo 27.2 ± 28.5; Bicirkan 22.3 ± 23.8; Total 24.4 ± 25.8; Anova NS **Delta D0/D7** / AVE ± Sd: Placebo 21.3 ± 25.3; Bicirkan 11.5 ± 24.9; Total 15.8 ± 25.3; Anova NS **Delta D0/D14** / AVE ± Sd: Placebo 28.0 ± 23.3; Bicirkan 27.6 ± 25.5; Total 27.8 ± 24.3; Anova NS **Delta D0/D21** / AVE ± Sd: Placebo 28.8 ± 23.9; Bicirkan 30.2 ± 24.1; Total 29.6 ± 23.7; Anova NS Repeated measures analysis of variance: Treatment anova: 0.05 p-value: 0.8295 Significance: NS Time anova: 39.67 p-value: 0.0000 Significance: <0.0001 Treatment x time anova: 1.37 p-value: 0.2541 Significance: NS Identical analyses were performed to compare the change in the other functional signs, and do not show any significant differences either. The results from the per-protocol analysis were exactly superimposable on those obtained in the ITT set. 8 patients (6 in the placebo group and 2 in the Bicirkan group) out of the 52 patients analysed for safety experienced at least one adverse event. The majority were mild to moderate and only one SAE was reported in the placebo group (gastroenteritis). Tolerance to Bicirkan appeared to be good and comparable to that of the placebo.
Conclusion	**This study did not demonstrate benefit from Bicirkan compared to the placebo on painful discomfort of venous origin, experienced by obese female patients or on any of the other functional signs they experienced. The tolerability of Bicirkan was comparable to Placebo**