SERVIER s.r.o.

Document title	**CLINICAL STUDY REPORT**
Study title	Detralex® versus placebo in the treatment of acute haemorrhoids in patients with acute haemorrhoidal attack - HEMODEX study. One week, double-blind, randomized, placebo-controlled multicentre study.
Test drug code	S5682 - Diosmin 450 mg, flavonoids expressed as hesperidin 50 mg (Detralex®)
Indication	Acute hemorrhoidal attack
Development phase	IV
Protocol code	IC4-05682-031-CZE
Study initiation date	01/2005
Study completion date	06/2005
Main coordinator	[redacted]
Sponsor	Servier s.r.o. Florentinum Na Florenci 2116/15 110 02 Prague 1 Czech Republic
Responsible person	[redacted]
GCP	This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.
Date of the report	25th September 2017
Version of the report	Final version

~~**CONFIDENTIAL**~~

SYNOPSIS

Name of Sponsor: Servier s r.o., Florentinum, Na Florenci 2116/15, 110 02 Prague 1		
Test drug **Name of Finished Product: Detralex®** **Name of Active Ingredient:** S5682		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: Detralex® versus placebo in the treatment of acute haemorrhoids in patients with acute haemorrhoidal attack - HEMODEX study. One week, double-blind, randomized, placebo-controlled multicentre study. Protocol No.: IC4-05682-031-CZE EudraCT No.: 200400270732		
National coordinator [redacted]		
Study centres: 24 centres located in the Czech Republic included at least one patient.		
Publication (reference): *None*		
Studied period: Initiation date: 01/2005 Completion date: 06/2005	**Phase of development of the study**: IV	
Objectives: Primary: Comparison of anitis, bleeding (reduction of bleeding, cessation of bleeding) and pain due to acute hemorrhoidal attack between Detralex® and placebo. Secondary: Reduction of the other signs and symptoms of acute hemorrhoidal attack (comparison between Detralex® and placebo).		
Methodology: One week, randomized, double-blind, placebo controlled, multicentre study. Duration of study: 1 week of treatment. 3 visits (D0, D4 and D7) were organised during study. This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.		
Number of patients: Planned: total: 150 (75 in each group) Included: 148 (74 in the Detralex group, 74 in the placebo group)		
Main inclusion criteria: - Male and female adults between 18 and 60 years; - Presenting an acute hemorrhoidal episode of recent onset (48 hours at maximum): • Stage I, II, III • Established by anoscopy examination • Presenting with a grade of at least 3 (i.e. blood on feces, in toilet bowl) and/or **anitis** with a grade of at least 3 (moderate) on a 4-point scale rating from 1 to 4 at examination. **Main exclusion criteria:** - Patient presenting hemorrhoidal manifestations requiring acute surgery; - Presenting hemorrhoidal associated with an anal fissure; - Presenting permanent prolapsed hemorrhoids (stage IV); - Patient having already received venotonics, anticoagulant, antiplatelet; - Analgetic or antiinflammatory treatment for ongoing episode; - Patient receiving topical hemorrhoid treatment for ongoing episode.		

Test drug:
Detralex® 500 mg oral tablets containing: micronized purified flavonoid fraction (MPFF) - diosmin 450 mg, flavonoids expressed as hesperidin 50 mg.
Patients were to receive 3 tablets 2 times daily (6 tablets/day) for 4 days, then 2 tablets, 2 times daily (4 tablets/day) for 3 days.

Comparator (placebo):
Placebo tablets. Patients were to receive 3 tablets 2 times daily (6 tablets/day) for 4 days then 2 tablets, 2 times daily (4 tablets/day) for 3 days.

Study periods:
Run-in period: none
Treatment period: 1 week
Wash-out / follow-up period: none

Criteria for evaluation:
Primary:
The global efficacy of the treatment was evaluated on the following main criteria:
- **Bleeding**: reduction of bleeding, cessation of bleeding. Evaluation of bleeding by the investigator as referred by the patient using a 4-point rating scale: NO, YES and if YES 1= soiling, 2=blood on paper by wiping, 3=blood on feces, toilet bowl.
- **Anitis**: bulging, blush, warming, pain, impaired function. Evaluation by the investigator after anoscopy using a 4-point rating scale: 1=absent, 2=mild, 3=moderate, 4=severe.
- **Pain**: Visual Analogue Scale (VAS) in the patient's diary.

Secondary:
- Anal discharge: evaluated by the investigator as referred by the patient (a 4-point rating scale) at visits.
- Itching: VAS in the patient's diary,
- Sensation of tension: VAS in the patient's diary,
- Medication intake: number of paracetamol tablets taken (in the patient's diary).
- Overall appreciation of therapeutic activity evaluated by the investigator by comparison of the observation performed at D4 and D7 with regard to D0, (4-point scale).
- Global efficacy of the treatment: evaluated by the patient and investigator.

Statistical methods: The statistical analysis was carried out by Servier, s r.o. in Czech Republic.
Descriptive statistics were provided for study outcome and safety.
Efficacy and safety were evaluated over the period D0 - D7 and compared between the two treatment groups.
The statistical software SYSTAT was used, all tests were two-sided and the significance level was fixed at 5%.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Patients disposition

	Detralex	Placebo	All
Included	74	74	148
Withdrawn due to	0	0	0
- lost to follow-up	0	0	0
- adverse event	0	0	0
- non-medical reason	0	0	0
- protocol deviation	3	3	6
Completed	71	71	142
Per Protocol Set (PPS)	71	71	142

Safety analysis was performed on patients having received at least one dose of treatment.
Baseline characteristics and efficacy results are presented hereafter on the population of patients with no major protocol deviations (PPS = 142).

BASELINE CHARACTERISTICS

Baseline characteristics in the PPS (N =142)

		Detralex (N = 71)	Placebo (N = 71)
Gender			
Men	n (%)	32 (45.1%)	28 (39.4%)
Women	n (%)	39 (54.9%)	43 (60.6%)
Age	mean ± SD	41 ± 12.6	45 ± 11.5
	min;max	17;68	19;65
Weight	mean ± SD	77 ± 13.9	81 ± 13.2
	min;max	50;103	57;115

Baseline characteristics were well balanced between the two treatment groups.

COMPLIANCE TO TREATMENT

Compliance in the PPS (N =142)

		Detralex (N = 71)	Placebo (N = 71)
Compliance at D4	mean ± SD	100.3 ± 2.2	100.1 ± 1.8
	min;max	96;113	93;113
Compliance at D7	mean ± SD	100.8 ± 6.6	99.5 ± 6.3
	min;max	75;133	50;77

The compliance was satisfactory and well balanced between the two treatment groups.

EFFICACY RESULTS

Efficacy - summary

Primary assessment criteria

Bleeding

The frequency of patients with bleeding is presented in the Table below. A significant decrease was observed over the 7-day treatment in each treatment group with no statistically significant difference between groups.

Bleeding (PPS: N =142)

		Detralex (N = 71)	Placebo (N = 71)
D0	n (%)	55 (77.5%)	60 (84.5%)
D4	n (%)	22 (31.0%)	29 (40.8%)
D7	n (%)	11 (15.5%)	16 (22.5%)
Evolution over time	p	0.002	0.008
Between-group difference		NS	

The same results (*i.e.* improvement over time with no difference between treatment groups) were observed for other parameters, as follows:

- Cessation of bleeding: 33 (60 %) patients in the Detralex® group, 32 (53.3 %) in the placebo group at D4; 46 (83 %) patients in the Detralex® group, 46 (77 %) in the placebo group at D7 (between-group difference *NS).*
- Cessation of bleeding in the patients who were bleeding at D0: in the Detralex® group 60 % of patients at D4, 84 % of patients at D7 visit; in the placebo group 53 % of patients at D4 and 77 % at D7 (between-group difference *NS*).

Anitis

Anitis: number of patients with improvement in the four point scale rating (from 1 to 4)

- at D4 visit: 57 patients out of 71 patients (Detralex® group); 50 patients out of 71 (placebo group) (between groups difference *NS);*
- at D7 visit: 64 patients out of 71 patients (Detralex® group); 59 patients out of 71 (placebo group) (between groups difference *NS);*

Results were close or similar for improvement in components of anitis: bulging, blush, warming, pain, impaired function.

Pain

Results did not show any significant difference between treatment groups, except on the first day of treatment. Pain was reduced from D0 morning (before treatment) to D0 evening, from 4.4 to 3.8 in Detralex® group (p=0.003) and from 3.8 to 3.7 in the placebo group (p=0.560); the between group difference was statistically significant (p=0.074).

Overall, a significant improvement over time was observed for the primary endpoints, with no between-group difference. However, the number of patients with disappearance of symptoms of anitis or bleeding at D7 (vs D0) was 21 (29.6 %) patients in Detralex® group and 10 (14.1 %) patients in placebo group. The between-group difference was statistically significant (p=0.025). The relative risk to have none of the above-mentioned symptoms at D7 visit was 2.1 times higher for a patient treated with Detralex® than for a patient on placebo (relative risk=2.1 and IC95 % (1.07; 4.14)).

Secondary assessment criteria

A significant improvement over time was observed for secondary endpoints, with no between-group difference.

SAFETY RESULTS

No relevant changes were reported in weight, blood pressure and heart rate over the treatment period in any treatment group.

One non-serious adverse event was reported (respiratory infection) in one patient treated with Detralex®. This adverse event was considered not related to the study drug by the investigator, was graded as mild and did not lead to study termination or study drug withdrawal. No other adverse event was reported in any treatment group.

CONCLUSION

Overall, symptoms of patients with haemorrhoidal attack were markedly improved over the 7-day treatment period, with no statistically significant benefit of Detralex® over placebo. Detralex® was well tolerated with no effects on vital signs or any relevant adverse effect.

Date of the report: 25. 9. 2017

Version of the report: Final version