FUNCTIONAL VENOUS INSUFFICIENCY:
COMPARATIVE CLINICAL TRIAL OF DIOVENOR® 600 MG¹ (600 MG OF SEMI-SYNTHETIC DIOSMIN) ONCE A DAY VERSUS A 500 MG FLAVONOID MIXTURE (900 MG OF DIOSMIN) TWICE A DAY

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INTRODUCTION
Chronic venous insufficiency includes painful functional signs, such as heavy legs, phebalgia (pain along the veins), restless leg syndrome (impatience) and orthostatic oedema (2). These symptoms are particularly noticeable in post-phlebitic syndrome and in most individuals with primary varicose veins. Similar discomfort may also occur in the absence of any specific disease of the main superficial and deep veins, particularly due to work-related positional factors (prolonged seating position, shuffling) and physical (ambient heat) and hormonal factors (3). A large number of indirect arguments (individual variability, associated vasomotor disorders, and Doppler ultrasound abnormalities) suggest that microcirculation is responsible for generating these symptoms.
The active ingredient of Diovenor® 600 mg is semi-synthetic diosmin, and its practical advantage is that it can be taken once. Its pharmacological properties have been established since 1978 when it was first introduced on the market for its phlebotonic, vasculoprotective and anti-inflammatory activities. Its vasculoprotective effect was objectified on the physical or chemical induction of the capillary resistance (1). Its anti-oedematous effect can be compared to its anti-inflammatory action: lipoxygenase inhibition, leukocyte migration and anti-complement action.
In order to consolidate the results obtained on the efficacy of Diovenor® 600 mg in the treatment of functional venous insufficiency in non-hospital-based practice, we conducted a multicentre, double-blind clinical trial with Diovenor® 600 mg taken once a day versus an association of 500 mg of flavonoids including 90% of diosmin taken twice a day.

PATIENTS AND METHODS
This multicentre, comparative, randomized, double-blind clinical trial with Diovenor® 600 mg taken once a day versus an association of 500 mg of flavonoids including 90% of diosmin taken twice a day to measure the efficacy on functional disorders of venous insufficiency in the lower limbs was performed by 9 angiology medical professionals.
The doctors had to include 72 female patients aged between 18 and 45 years, on oral contraception, who had been suffering for at least 6 months from painful and/or heavy legs sufficiently intense (rated at minimum 2) to alter their quality of life significantly. These women had to present at the moment of inclusion with functional symptoms of venous insufficiency without any haemodynamic abnormalities that were clinically significant (varicose vein) or superficial and deep as visualised in continuous-wave Doppler ultrasound.
This protocol was granted a favourable opinion by the Consultation Committee for the Protection of Individuals participating in Biomedical Research (CCPPRB) of Caen on 15 March 1993. All patients included had to provide their informed and written consent.
The following patients could not be included:

- Suffering from venous insufficiency without any haemodynamic abnormalities that were significant either clinically (varicose vein) or on Doppler ultrasound (valvular, ostial or deep vein incontinence)
- Taking a cardiovascular, analgesic, anti-inflammatory treatment or vitamin C or any other phlebotonic therapy
- Having taken analgesic medication or any other phlebotonic therapy for less than 48 hours or 1 month respectively before inclusion
- With elastic compression stockings
- Suffering from clinical neuropathy, symptomatic lumbar osteoarthritis, plantar static disorders, stage II, III, IV arteriopathy or permanent oedema of vascular or general origin
- Having presented with trauma to the lower limbs within 6 months prior to the start of the trial
- Having presented with reactions of intolerance to diosmin

**TREATMENTS**

This trial was performed double-blind since the objective was to determine the therapeutic efficacy on the functional symptomatology. Since this methodology requires the double placebo technique, both groups needed to take the treatment twice a day ‘symmetrically’, namely morning and evening. The patients had to take 3 tablets a day:

- For the Diovenor® 600 mg group, the daily dosage was 1 tablet of Diovenor® 600 mg in the morning and 1 placebo tablet of 500 mg of flavonoid mixture including 90% of diosmin morning and evening
- For the control group, the daily dosage was 1 placebo tablet of Diovenor® 600 mg in the morning and 1 tablet of 500 mg of flavonoid mixture including 90% of diosmin morning and evening

**ASSESSMENT CRITERIA**

**THE PRIMARY EFFICACY OUTCOME MEASURES WERE:**

- Assessment of the heaviness/pain in the patient's legs using a vertical analogue visual scale of 100 mm describing the painful sensations or heaviness in the legs. This parameter was recorded on D0, D7, D14, D21 and D28 on a self-assessment sheet.
- Doctor assessment of the functional symptomatology (before and after 1 month of treatment). This index includes the sum of all grades of the different symptoms:
  - Painful and/or heavy legs
  - Sensation of oedema in the lower limbs
  - Paraesthesia (impatient, restless legs)

Each symptom if graded from 0 (absent) to 3 (significant and severely altering the quality of life of the patient).

**THE SECONDARY EFFICACY OUTCOME MEASURES WERE:**

- Overall decision by the doctor who assesses treatment suitability to the clinical situation at the end of trial (perfectly adapted, well adapted, moderately adapted, not at all adapted)
- Overall decision by the patient who assess her degree of satisfaction with the treatment (very satisfied, satisfied, moderately satisfied, not at all satisfied)

**ASSESSMENT OF TOLERANCE**

This is dependent on the collection of undesirable events at the end of the trial that were spontaneously reported by the patients.
STATISTICAL ANALYSIS

- The homogeneity of the groups was analysed with:
  - The chi-square test or the Fisher’s exact test in the case of insufficient patient numbers for the qualitative parameters
  - Variance analysis or the Kruskal-Wallis one-way analysis of variance for the quantitative parameters
- For the efficacy outcome measures, the tests used were:
  - Variance analysis (ANOVA) on the differences (D0-D28) for the global index of functional symptomatology
  - Variance analysis for the repeated measurements on the differences (D7-D0), (D14-D0), (D21-D0), (D28-D0) for the self-assessment of the patient’s pain
  - The Kruskal-Wallis one-way analysis of variance for the secondary outcome measures: overall doctor assessment and overall patient assessment
- Analysis of tolerance was only descriptive

RESULTS

DESCRIPTION OF POPULATION

69 female patients out of the 72 initially anticipated by the protocol (34 patients in the Diovenor® 600 mg group and 35 patients in the control group) were included due to the imperative closing period of inclusions.

The two treatment groups were comparable in all demographic parameters (average age of 30 years, active workers, suffering from functional venous insufficiency manifestations for the past 6 to 7 years, family history of varicose veins in over 80% of cases) and assessment criteria (assessment of functional symptomatology by the doctor and self-assessment of pain by the patient).

THERAPEUTIC RESULTS

The primary outcome measures

Self-assessment of the pain/heaviness in legs done using a visual analogue scale completed by the patient was comparable between the two treatment groups. A significant decrease (p < 0.0001) in the pain was observed in both groups, though there was a more significant intra-group improvement after 1 week of treatment in the control group and after 1 month of treatment in the Diovenor® 600 mg group respectively. These differences between both groups are nevertheless no significant (figure 1).

The index of functional symptomatology assessed by the doctor is improved overall after 1 month of treatment in both groups, without any statistically significant difference between groups (figure 2).

The secondary outcome measures

Overall doctor assessment at the end of the trial was the same in both therapeutic groups, namely treatment perfectly adapted or well-adapted to the clinical situation in 64.7% of cases.

Overall patient assessment was comparable in both treatment groups, slightly in favour of the Diovenor® 600 mg group with 58.8% of women very satisfied and satisfied, versus 48.6% in the control group (figure 3). This satisfaction index did not consider the single daily intake since the study used the double placebo technique.
Fig. 1 – Evolution of self-assessment of pain by the patient (Dt-D0) in each treatment group

Fig. 2 – Evolution of overall index of functional symptomatology in each treatment group
Assessment of tolerance
The number of undesirable events reported by the patient was very low:
- 4 undesirable events concerning 3 patients in the Diovenor® 600 mg group (vomiting associated with intermittent diarrhoea, gastralgia, headaches) including 1 trial withdrawal due to vomiting and diarrhoea
- 6 undesirable events concerning 5 patients in the control group (constipation and abdominal bloating, 3 cases of gastralgia, nausea) including 2 trial withdrawals at the request of patients due to gastralgia

DISCUSSION
The methodology of this trial was that of a randomized, comparative, double-blind trial since the main objective was therapeutic efficacy. The acceptability of a single intake of Diovenor® 600 mg compared with two daily intakes of 500 mg of the flavonoid mixture including 90% of diosmin therefore could not be assessed because all patients had to take two tablets every morning and one tablet in the evening to comply with double-blind methodology.

The results are obtained with both Diovenor® 600 mg once a day and 500 mg of the flavonoid mixture including 90% of diosmin twice a day revealed a very noticeable efficacy in the clinical and functional symptomatology related to venous insufficiency of the lower limbs.

The clinical symptoms aetiology was assessed in two ways:
- Doctor assessment of an overall score of the functional symptomatology and his/her overall assessment of the efficacy and tolerance of the treatment at the end of the trial. The overall score was a qualitative criterion, including the sum of the grading of three main symptoms of functional venous insufficiency of the lower limbs, specifically pain and/or heaviness, paraesthesia and oedema.
Overall doctor assessment was a qualitative criterion enabling the practitioner to assess the overall therapeutic activity.
• Patient assessment through the visual analogue scale and the overall assessment concerning her satisfaction with the treatment. The patients used a visual analogue scale to self-assess and quantify the degree of pain/heaviness in the legs. This type of assessment performed weakly by the patient is enabled and analysis of the efficacy dynamics by objectifying a comparable improvement for both treatment groups studied.

Self-assessment is a method that is all the more interesting as it enables data collection that is separate from the doctor-patient relationship and it stimulates treatment compliance by motivating patients to actively participate in treatment assessment.

The different assessment criteria enabled to show a significant improvement in the functional symptomatology after one month of treatment with Diovenor® 600 mg once a day versus 500 mg of the flavonoid mixture including 90% of diosmin twice a day. The intergroup analysis of the therapeutic activity did not objectify any significant difference between the two treatment regimens. It should be noted that patients sometimes resorted to the occasional use of analgesics (specifically paracetamol, and the only analgesic permitted by the protocol) and anti-inflammatories. Use of these drugs was more often short-term (one to two days and always under seven days) and equally distributed in both groups.

This use of analgesics and anti-inflammatories did not alter the therapeutic results. This paradox is undoubtedly explained by the fact that these drugs were prescribed in most cases for conditions of non-vascular origin (minor ENT conditions, dental pain or rheumatology pain) regardless of the therapeutic assessment and generally within the first two weeks of the trial.

Tolerance of treatment proved satisfactory in both groups, though a greater frequency of undesirable events with a single dose of 600 mg of semi-synthetic diosmin compared with two daily doses of 450 mg of diosmin was a concern.

CONCLUSION
This phase III, multicenter, controlled, randomized, double-blind clinical trial of Diovenor® 600 mg once a day and 500 mg of the flavonoid mixture including 90% of diosmin twice a day involved 69 patients all on oral contraception and suffering from functional disorders of venous and lymphatic insufficiency, specifically pain and/or heaviness in legs sufficiently intense to significantly alter the quality of life of patients. The efficacy of the functional symptomatology of the two therapeutic regimens, the main parameter studied, was assessed by the doctor (overall index of functional symptomatology, overall assessment) on the one hand and by the patient (visual analogue scale, overall assessment) on the other.

The results obtained concerning the efficacy outcome measures on the functional symptomatology enabled to conclude that the efficacy of Diovenor® 600 mg (or 600 mg of semi-synthetic diosmin once a day) was comparable with that of the control group (500 mg of flavonoids including 90% of diosmin twice a day, or 900 mg of diosmin). Tolerance proved satisfactory in both groups with few undesirable events that were mainly of digestive nature (in particular, gastralgia).

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