



## Original Articles

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# Treatment of chronic venous insufficiency with Aesculaforce Vein Gel\*

**Clinical study to demonstrate the efficacy and tolerability of an herbal vein treatment**

**C**hronic venous insufficiency (CVI) is a disease of the veins that occurs with high prevalence in the adult population. The disease arises from mechanical impairment of the venous return, which is caused by venous occlusion or valve failure of the superficial veins in combination with that of connecting veins or deep veins.

The associated increased filtration of fluids, electrolytes and low molecular proteins into the tissue interstitium causes the development of oedema in the ankle and calf regions. In order to prevent the development of Stage III (according to Widmer) of crural ulcers, it is important to treat CVI adequately in stage I (oedema and corona phlebectatica paraplantis or cockpit varices) or in stage II (additional trophic nutritional disorders of the skin). Among the most important therapeutic measures are compression therapy and drug therapy with veno-tonic drugs, which include horse chestnut seed extract (HCSE). As shown in a paper published by DIEHM [1], treatment with HCSE provides a true alternative to compression therapy.

Aescin, the main constituent of

Aesculaforce Vein Gel, a vein treatment prepared from fresh horse chestnuts, was investigated in a non-controlled multicentre study in 71 patients with chronic venous insufficiency with consequent oedema. During the 6-week treatment, the circumference of the ankles was reduced statistically significantly by 0.7 cm and the sum of the symptom score fell by 60%. The severity of the individual symptoms was also significantly reduced. The vein gel was considered to be good or moderately effective in over 85% of the cases. Tolerability was always very good and none of the adverse events that occurred was causally related to the study drug.

HCSE, has an anti-oedematous and capillary "sealing" effect in various experimental models. According to Monograph E [2], there are indications that HCSE reduces the activity of lysosomal enzymes which is increased in chronic venous disease and thus prevents the breakdown of the glycocalyx in the region of the capillary wall. Filtration of small molecular proteins, electrolytes and water into the interstitium is reduced by reduction of vascular permeability and the development of oedema is prevented. HCSE has, in addition, a venotonic effect.

Capillary sealing, anti-oedematous and venotonic effects of orally administered HCSE has been demonstrated in numerous placebo-

controlled, double-blind studies, including a study with Aesculaforce film-coated tablets [3].

To provide in addition to the oral oedema therapy with the gastrically tolerated Aesculaforce film-coated tablets, Bioforce has developed a new gel that contains an extract from the seeds of horse chestnut (*Aesculus hippocastanum* L.) and is standardised to 2% of aescin. The aim of the present study was to investigate the efficacy and safety of this Aesculaforce Vein Gel.

### Study design and patients

This non-controlled, multicentre study was carried out from June to



October 1997 by 8 General Practitioners in Baden-Württemberg (Germany) under the leadership of Dr. med. Thomas Jung (Deggingen, FRG). To ensure data quality according to the Good Clinical Practice (GCP) Guidelines, it was monitored by the L.A.B company, Neu Ulm (FRG).

61 women and 10 men aged between 20 and 91 years participated in the study. They were suffering from CVI-induced oedema. During the 6-week treatment period the patients were instructed to apply the vein gel every morning and evening to the lower part (including the ankle) of both legs and to the inner surfaces of the thighs. They were to visit the investigator after 3 weeks for follow-up (second visit) and after 6 weeks for a final examination (3rd visit).

The following were exclusion criteria: leg ulcers, acute phlebitis or phlebothrombosis, lymph oedema, inflammatory skin changes, a condition following stripping of the varicose veins, simultaneous compression therapy, simultaneous treatment with other topical drugs for the legs, oral vein therapy that has been carried out less than 4 weeks prior to this study, diabetes mellitus and life-threatening diseases.

To assess the efficacy, the ankle circumference and the total symptom score were measured at the 2nd and 3rd visits and at the 3rd visit the overall efficacy was assessed by doctors and patients. The ankle circumference was measured to 0.1 cm precisely using a tape measure directly above the ankle. The total symptom score consisted of the gradation of the symptoms oedema, heavy, tired legs/feeling of tension, leg pain, burning sensations in the legs, itching and paraesthesia on a 6-point scale (not present, mild, moderate, marked, severe, extremely severe). Assessment of overall activity was carried out with a 4-level scale (good, moderate, slightly active, inactive).

To analyse the efficacy, the ankle circumference and total symptom score or scores for the individ-

ual symptoms at visits 1 and 3 were compared using the Wilcoxon sign-rank test (significance level = 0.05 for a one-tailed test, i.e. halving the p value of the two-sided test). In addition, the same parameters were compared for the 1st and 2nd visits and for the 2nd and 3rd visits.

Assessment of the tolerability of the study preparation was carried out at the final visit by both the investigator and the patient. In addition, all adverse events (AEs) were recorded and the patients' acceptance of the study preparation was asked for.

Out of the 71 patients treated, 7 did not complete the study according to protocol. One patient withdrew his consent at short notice, in one case the study medication was withdrawn at the patient's request after a moderate AE. Two patients stopped the study prematurely because of serious AEs. Two of the patients had diabetes mellitus, which was an exclusion criterion and one patient was treated for more than 7 weeks.

To assess the tolerability, the results of the intention-to-treat analysis in which all the patients enrolled in the study were evaluated, was used. The total group was also used for the descriptive assessment of efficacy. The confirmatory assessment of efficacy was based, on the other hand, only on the per protocol evaluation in which only the cases that conformed to protocol were taken into account.

## Results

### Compliance

Compliance was exceedingly high with 99% (from the first to the second visit) and 98 % (from the second to the third visit). None of the patients exhibited unsatisfactory compliance (< 70%).

### Efficacy

The results of the per protocol evaluation differ only extremely slightly from those of the intention-

to-treat analysis. We shall therefore restrict ourselves in the following presentation of results to the per protocol evaluation which serve for confirmation of the assessment of efficacy.

The **ankle circumference** was reduced in the course of the 6-week treatment by a statistically significant amount of 0.7 cm on average ( $p < 0.001$ ). The reduction of the ankle circumference was also clear from visit 1 to visit 2 and from visit 2 to visit 3 ( $p < 0.001$ ) (Fig. 1).

The **total symptom score** fell statistically significantly by 60% by the end of the treatment ( $p < 0.001$ ). The reduction was clearly seen in both the first and second halves of the treatment ( $p < 0.001$ ) (Fig 2).

The **scores for individual symptoms** were also statistically significantly reduced in the course of the 6-week treatment. The severity of the symptoms oedema, heavy, tired legs/ feeling of tension and leg pain fell from moderate or moderate to marked to mild. The symptoms burning in the legs, itching and paraesthesia were only slightly present at the start of treatment or were only mild or not present at all (Table 1).

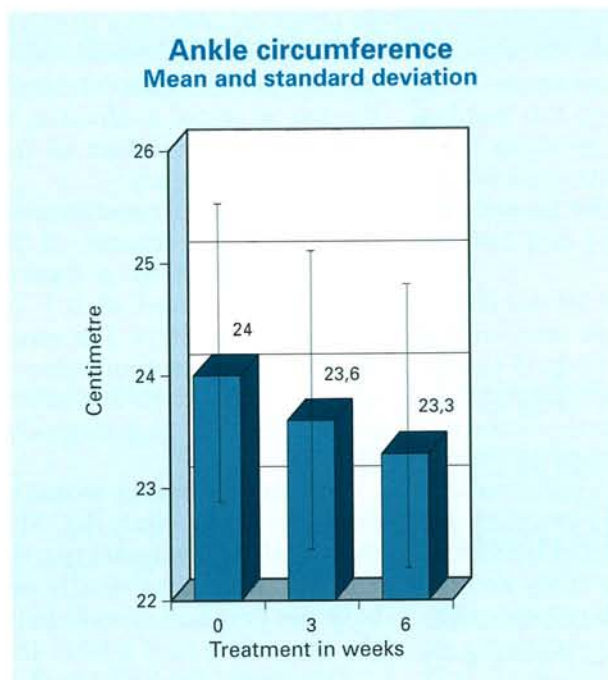
The overall efficacy of the study medication was assessed by the patients almost the same as by the investigators. They considered Aesculaforce Vein Gel to be efficacious in 97% and 98% of the cases respectively. In over 85% it was even good or moderately active (Fig. 3).

### Tolerability

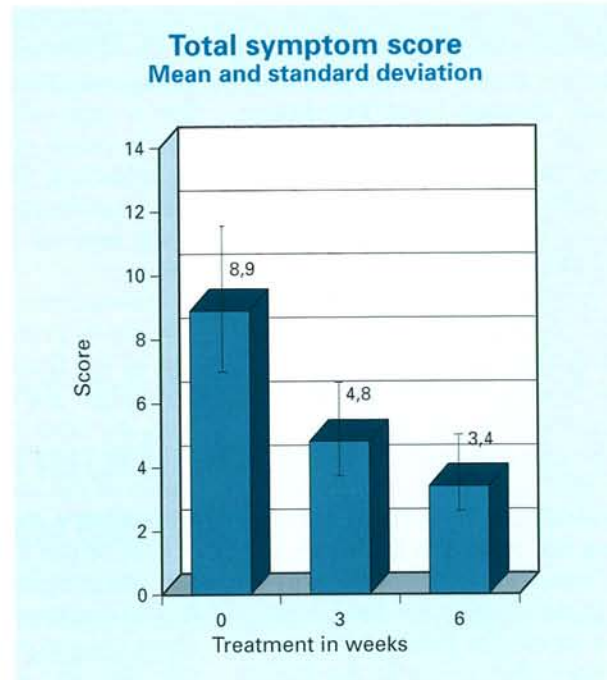
The tolerability of the vein gel was assessed as good in 97% by the investigators and in 92% by the patients (Fig. 4). No data was available for 2 patients. 75% of the patients would use the vein gel again if necessary.

A total of 18 adverse events (AEs) occurred in 13 patients (18%) (Table 2). The most frequently affected systems were the body as a whole, the nervous system, the psychological state, gastro-intestinal tract and skin, whereby none of





**Fig. 1:** Clinical study with Aesculaforce Vein Gel in patients with chronic venous insufficiency (Group analysed n = 64), Mean ankle circumference in the course of treatment



**Fig. 2:** Clinical study with Aesculaforce Vein Gel in patients with chronic venous insufficiency (Group analysed n = 64), Mean total symptom score in the course of treatment

Symptoms	Score (Mean $\pm$ standard deviation)			Wilcoxon signed rank test (p value)		
	Visit 1	Visit 2	Visit 3	Visit 1 vs. Visit 3	Visit 1 vs. Visit 2	Visite 2 vs. Visite 3
Oedema	2,0 $\pm$ 0,9	1,3 $\pm$ 0,9	1,0 $\pm$ 0,8	p < 0,001	p < 0,001	p < 0,001
Heavy tired legs/ / tension	2,5 $\pm$ 1,0	1,4 $\pm$ 0,9	1,0 $\pm$ 0,8	p < 0,001	p < 0,001	p < 0,001
Leg pain	2,2 $\pm$ 1,2	1,2 $\pm$ 1,1	0,8 $\pm$ 0,8	p < 0,001	p < 0,001	p < 0,001
Burning in legs	1,0 $\pm$ 1,3	0,5 $\pm$ 0,8	0,3 $\pm$ 0,5	p < 0,001	p < 0,001	p = 0,0015
Itching	0,7 $\pm$ 1,2	0,2 $\pm$ 0,5	0,2 $\pm$ 0,5	p < 0,001	p < 0,001	p = 0,271
Paraesthesia	0,5 $\pm$ 1,1	0,3 $\pm$ 0,7	0,2 $\pm$ 0,5	p = 0,0015	p = 0,015	p = 0,055

**Table 1:** Clinical study with Aesculaforce Vein Gel in patients with chronic venous insufficiency (Group analysed n = 64), Symptom scores (mean  $\pm$  standard deviation) and p-values of Wilcoxon's signed rank test

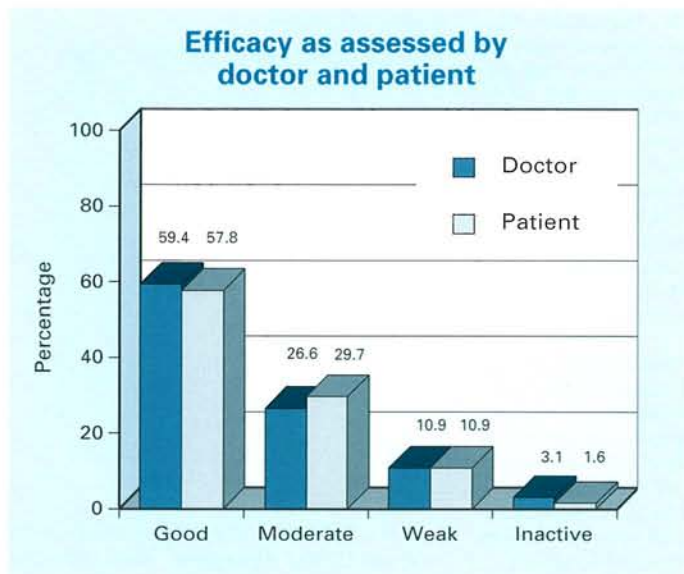
the AEs affecting the skin occurred where the study medication was applied. This involved eczema on the upper arm, an allergic reaction at the hair base and itching and blister formation on the neck.

The investigators assessed the causal relationship between the AEs and the study medication as

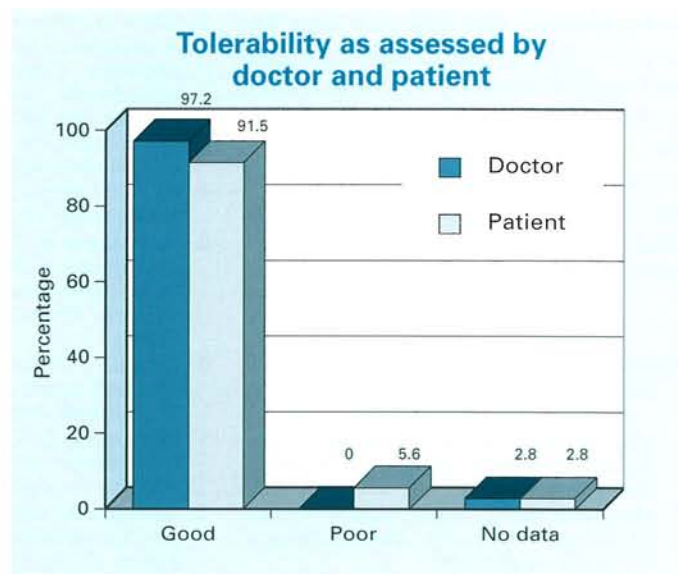
doubtful or unlikely in all cases. In the majority of cases there was in their opinion no relationship at all with the use of the vein gel.

The AEs were mostly mild or moderate in severity. There were, however, 3 serious AEs. One patient with tinnitus had to undergo infusion therapy, one patient was

hospitalised because of transitory ischaemic attacks with hypertensive derangement and one patient suffered cardiac arrest as the result of coronary heart disease. The investigators emphasised that these cases were also not related causally to the study medication.



**Fig. 3:** Clinical study with Aesculaforce Vein Gel in patients with chronic venous insufficiency (Group analysed n = 64), Therapeutic efficacy as assessed by doctor and patient



**Fig. 4:** Clinical study with Aesculaforce Vein Gel in patients with chronic venous insufficiency (Group analysed n = 71), Tolerability as assessed by doctor and patient

## Discussion and Conclusions

The present study results confirm the good efficacy of Aesculaforce Vein Gel. The ankle circumference was reduced in the course of 6 weeks' treatment by 0.7 cm, which was not only statistically significant but also a clinically relevant result. The severity of the symptoms was reduced by 60% and both the investigators and the patients assessed the vein gel in

the majority of cases as good or moderately effective.

A comparison with the following results from four other studies shows that the results obtained cannot be explained as a placebo effect and the vein gel is equivalent to oral treatment with HCSE or with a commercially available anti-oedemic preparation. In a 6-week study the ankle circumference was reduced by 0.5 cm with Aesculaforce film-coated tablets, whereas it remained unchanged with placebo

[3]. In two further placebo-controlled studies, a 4-week oral treatment with HCSE led to a reduction of the ankle circumference of 0.7 cm in comparison with a reduction of 0.3 cm or an increase of 0.1 cm with placebo [4, 5]. A four-week treatment with HCSE produced the same reduction of ankle circumference of 0.4 cm as a commercially available anti-oedema product [6].

Aesculaforce Vein Gel proved to be very well tolerated. The relationship of the AEs to the preparation was not at all, unlikely or doubtful. In addition, none of the AEs affecting the skin occurred at the site of application. Side effects can therefore be almost completely ruled out.

From the present results, therefore, it can be concluded that the Aesculaforce Vein Gel is very well tolerated, well accepted and leads to a clinically relevant reduction of CVI-induced complaints. Aesculaforce Vein Gel therefore represents a low risk, well-accepted alternative to chemically synthesised vein drugs and compression stockings.

As two clinical studies with aescin-containing preparations

Organ system	Causal relationship and severity			Total
	Mild	Doubtful or unlikely Moderate	Severe	
Whole body	1	2		3
Nervous system	2		1	3
Psychological state	1	2		3
Gastro-intestinal	1	2		3
Skin	3			3
Cardiovascular			2	2
Skeletal / muscle	1			1
	9	6	3	18

**Table 2:** Clinical study with Aesculaforce Vein Gel in patients with chronic venous insufficiency (Group analysed n = 71), Adverse events: Organ systems affected, causal relationship and severity



have shown, the efficacy can be improved by a combination of oral and topical therapy in comparison with topical therapy alone [7, 8]. We therefore recommend simultaneous treatment with Aesculaforce Vein Gel and Aesculaforce Film-coated Tablets for the treatment of mild to moderate CVI.

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