An Open Study to Assess the Safety and Efficacy of *Aesculus hippocastanum* Tablets (Aesculaforce® 50 mg) in the Treatment of Chronic Venous Insufficiency

Sylvia Dickson, BSc (Hons)
Julie Gallagher, MSc, BA (Hons), RN
Lorna McIntyre, BSc (Hons)
Andy Suter, MSc
Jen Tan, MBBS

ABSTRACT. An open study was carried out to assess, primarily, the safety and tolerability of *Aesculus hippocastanum* in the treatment of CVI. Patients underwent 8 consecutive weeks of treatment and were asked to take one 50 mg *Aesculus hippocastanum* tablet, twice daily. In total, 91 adverse events were reported, of which only 4 were rated as probably related to the study drug. Patients judged the tolerability of the study medication in the majority of the cases at visits 2 and 3 (90 and 95%, respectively) to be 'good' or 'fairly good.' Only 2 patients rated

Sylvia Dickson (E-mail: sylvia@bioforce.co.uk) and Lorna McIntyre (E-mail: lorna@bioforce.co.uk) are Clinical Researchers, Julie Gallagher (E-mail: julie@bioforce.co.uk) is Clinical Trial Department Manager, and Jen Tan (jen@bioforce.co.uk) is Director, Bioforce (UK) Ltd., 2 Brewster Place, Irvine, KA11 5DD, UK.

Andy Suter is Head of Medical Department, Bioforce AG, P.O. Box 76, 9325 Roggwil, Switzerland (E-mail: A.Suter@Bioforce.ch).

The authors sincerely thank all the patients who took part in the study and the study monitor for all his advice.

Journal of Herbal Pharmacotherapy, Vol. 4(2) 2004
http://www.haworthpress.com/web/JHP
© 2004 by The Haworth Press, Inc. All rights reserved.
Digital Object Identifier: 10.1300/J157v04n02_03

tolerability as poor at visit 3. For each of the symptoms investigated the difference in the median value between baseline and visit 3 was found to be statistically significant and both the ankle and lower leg circumference decreased. The PPG measurements were rejected after analysis since validation measurements carried out after the trial showed that the PPG technique had an internal error of around 30%. Nevertheless, the majority of patients rated efficacy to be 'very good' or 'good,' with only 10 patients reporting no effect by the end of the study. The results of this study indicate that Aesculaforce® 50 mg tablets are a safe, well-tolerated and efficacious treatment for Widmer stage I and II CVI. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <http://www.HaworthPress.com> © 2004 by The Haworth Press, Inc. All rights reserved.]*

KEYWORDS. Chronic venous insufficiency, Aesculaforce®, horse chestnut

INTRODUCTION

CVI is the term used to describe the impairment of venous return, which is the volume of blood flowing back to the heart, usually from the systemic veins in the legs. The impairment of venous return means that the blood flow back to the heart is insufficient in that it is not as fast or efficient as it should be. This results in oedema and may lead to leg ulcerations.[3]

A number of factors are thought to contribute to the pathophysiology of CVI. These include gravitational reflux, compartmental pressure and leucocyte trapping and activation.[1]

It has been identified that patients with CVI have a greater quantity of leucocytes within the microcirculation of the affected limb, in comparison to healthy patients. It is postulated that this greater accumulation and activation of leucocytes is responsible for the increased abundance of elastase and other toxic products and, consequently, injury to surrounding tissue. Over time, the increased leucocyte levels damage the microcirculation and produce venous leg ulcers.[1,4]

Physical examination demonstrates increased leg circumference, oedema and superficial varicose veins. In addition erythema, dermatitis, hyperpigmentation (due to stasis and haemolysis of trapped red blood cells) and skin ulceration are other typical symptoms.[1,5]

The horse chestnut tree (*Aesculus hippocastanum* L.), although native to southeast Europe, is now distributed worldwide. The large, glob-

ular brown seeds are the part of the tree that is used medicinally. Traditionally, they have been used to treat varicose veins, haemorrhoids, respiratory diseases, malaria and rheumatism. Today they are now recommended in the treatment of CVI and its associated symptoms.[6]

Overall, *Aesculus hippocastanum* has an anti-inflammatory, astringent and anti-oedema action. The anti-inflammatory action is due to the presence of flavonoids whilst the astringent properties are a result of the tannin content, which help to tone the vessel walls. Finally, aescin exhibits an anti-oedema action and can increase venous tone.[7] It has been shown that the saponin aescin can interfere with enzymatic proteoglycan degradation by inhibiting the action of the enzymes elastase and hyaluronidase. This action makes *Aesculus hippocastanum* effective in the treatment of CVI since raised levels of these enzymes have been reported in CVI patients.

The aim of this study was to investigate the safety, tolerability and efficacy of a new enteric coated *Aesculus hippocastanum* tablets, standardized to contain 50 mg of aescin.

PATIENTS, MATERIALS AND METHODS

Study Design

This was an open monocentric study carried out between July and October 2002. The duration of the trial for each participant was 8 weeks with patients attending 4 visits. The Bioforce Independent Research Ethics Committee (BIREC) granted full ethical approval on 20th March 2002 and clinical trial exemption approval was granted from the Medicines Control Agency on 8th May 2002. The study was conducted according to ICH GCP guidelines and in accordance with the ethical obligations of the Declaration of Helsinki. The main aim of the study was to gather data on the safety of Aesculaforce® tablets to generate descriptive summary statistics for use in planning any future trials. In addition, this study was carried out as supporting documentation in a regulatory application.

Patients

Inclusion Criteria

To be eligible for inclusion in the study each patient had to fulfill the following criteria: CVI as clinically determined by the study physician,

aged between 18 and 75 years and the patient had to sign a declaration of consent.

It should be noted that only one leg, which had to meet the inclusion/exclusion criteria, was studied throughout the trial. If a patient presented with both legs affected then the more affected leg was studied, again, as long as the inclusion/exclusion criteria was met.

Exclusion Criteria

Patients were not eligible for the study if they fulfilled one or more of the following criteria: patients with Widmer Stage III CVI (Ulcus cruris), acute phlebothrombosis, acute phlebitis, primary or secondary lymph oedema, non-venous, inflammatory skin diseases of the legs, peripheral vascular disease or a history of gastric and duodenal ulcers. Pregnant or lactating women were excluded. Patients who had taken other medication in another clinical trial in the month prior to enrolling into this study and patients who had a known allergy to *Aesculus* or one of the inactive ingredients were not allowed to participate. Patients on Warfarin therapy or concomitant therapy with diuretics, antihypertensives, any other preparations for varicose veins, concomitant use of compression stockings or other compression therapy and concomitant local physiotherapy in the treatment region were excluded. Finally, patients who had a severe concurrent illness such as serious cardiac, renal or liver disease, diabetes and malignant tumours as well as patients who had undergone major orthopaedic surgery to the affected limb in the past 12 months, or patients who had suffered previous severe trauma to the affected limb were excluded.

Treatment

Patients who met the inclusion criteria at the screening visit were assigned to receive 8 consecutive weeks of treatment of Aesculaforce® Tablets. They were enteric coated and contained a fresh plant extract from *Aesculus hippocastanum* seeds (drug extract ration (DER) 5.0-6.1:1). Each tablet was standardized to contain 50 mg of aescin and the dose was one tablet twice daily, morning and evening, with food. Each patient received one bottle containing 70 tablets at each visit. Patients were instructed to return their bottle of medication at their next visit so that compliance could be monitored.

Measurements

Safety

Safety was assessed as a primary parameter by the eliciting and recording of adverse events. Patients were asked questions relating to their well-being and the safety (local symptoms) of the treatment preparation.

Tolerability

Patients and researchers were asked to rate the tolerability of the Aesculaforce tablets using a 4-point scale at visit 2 (week 4) and visit 3 (week 8). The scale used the following categories: good, fairly good, quite good and poor.

Efficacy

Efficacy was explored as a secondary parameter by measuring changes in symptom scores. Other measures of efficacy included changes in the circumference of the ankle and of the lower leg and changes in venous blood circulation of the affected lower limb, measured using PPG. Assessments of efficacy were also made by both the patient and researcher.

Symptom Score

This was calculated on the basis of 6 symptoms indicative of status: sensation of heaviness or tension, pain, burning sensation, itching and paraesthesias. Patients rated their symptoms using a 4-point scale (0 = none, 1 = slight, 2 = moderate and 3 = severe).

Ankle/Lower Leg Circumference

To measure the circumference of the ankle and of the lower leg patients had to be in the sitting position and have their feet completely flat on the floor. The patient's ankle circumference had to be measured 12 cm from the ground. For measurement of the lower leg circumference, the greatest circumference of the lower leg had to be identified. Generally, this tends to be around 28 cm from the ground. The height where the maximum circumference had been measured was recorded in the

patient's Case Report Form (CRF) so that at future visits the circumference was measured at the same height.

Photoplethysmography

The PPG technique was developed in 1981 in Germany as a screening and diagnostic tool for venous insufficiency. It is a non-invasive procedure that is designed to record changes in the amount of blood in the superficial veins.[8]

Some literature states that PPG is suitable only for diagnosing and screening patients with suspected CVI,[9] whilst others state that it is also suitable for monitoring the efficacy of therapy.[8] In our study, we used the PPG method to explore efficacy.

Ankle and lower leg circumferences and PPG measurements were carried out at visits 1, 2 and 3.

General Assessments of Efficacy

Overall general assessments of efficacy were carried out by both the researcher and patient at visits 2 and 3.

An assessment of overall acceptance was made by the patient. This consisted of the question "Would you (the patient) use the Aesculaforce tablets again?" A yes or no answer was elicited.

Patients were requested to return any unused medication at each visit so that compliance could be monitored throughout the study.

Sample Size and Statistical Analysis

This study was undertaken to generate descriptive statistics for the planning of further trials of Aesculaforce tablets, if required at a later date, and as supporting documentation in a regulatory application. It was considered, based on other research trials, that a minimum of 50 completed patients would provide adequate data for this purpose. Data entry was carried out by the Clinical Trial Department at Bioforce (UK) Ltd. and D.S.H. Statistical Services, Rohrbach, Germany analysed the data using SAS, Version 6.12.

Results were generated for the PP, ITT and safety populations. The PP population comprised of the patients who (I) had a week 8 assessment (II) attended the week 8 visit within 5 days of the scheduled time and (III) had no other major protocol violations. Major protocol violations were defined as violation of any of the inclusion/exclusion crite-

ria. The ITT population comprised of all patients who received at least one dose of treatment and had at least one on-treatment safety and tolerability assessment. The safety population comprised of all patients who took at least one dose of the trial drug.

General descriptive statistics were performed on all variables, with the mean, median and standard deviation being calculated. For the data collected from the symptom score, ankle and lower leg circumference and the PPG technique, the changes between baseline and the end of the study were used as criteria for statistical evaluation. Since the data for each of these parameters was not normally distributed, the median values were statistically tested using the Wilcoxon signed rank test.

RESULTS

Patients

In total, 87 patients were enrolled into the study, the majority of which were female. There were no significant differences in age, symptom score, ankle and lower leg circumference at baseline between the different patient populations (Table 1).

In total, 84 patients were suffering from varicose veins, 1 with superficial thread veins, 1 with prominent veins and 1 with poor circulation. In the end, 75 patients completed the study and 12 dropped out prematurely. Fifty-one patients fulfilled all the study conditions and were entered into the PP population. Seventy-eight were entered into the ITT population and all patients were entered into the safety population.

Safety

Adverse Events

A total of 91 adverse events were reported during the treatment period from 57 patients, of which only 4 were rated as probably related to the study drug. The majority of patients experienced only one or two adverse events. Of all adverse events, none were assessed as serious.

Of the 4 adverse events rated as probably related to the study drug, 3 were rated as severe in nature and 1 mild. These were mild nausea experienced during the first few days of treatment, although the symptoms were not persisting, a "sore" stomach where symptoms disappeared after the daily dosage was reduced, "bad wind" and "stomach pain."

In total, 12 patients terminated their treatment prematurely of which 5 withdrew due to adverse events, which were rated moderate in nature.

TABLE 1. Demographic and diagnostic criteria of the study populations at visit 1.

	PP	ITT	Safety
Female	34	58	65
Male	17	20	22
Average age [years]	51.3 ± 12.2	51.7 ± 11.1	51.1 ± 11.0
Study leg			
Left Leg	18	29	34
Right Leg	33	49	53
Symptom score (mean, SD)			
Heaviness	1.6 ± 0.78	1.7 ± 0.79	1.7 ± 0.78
Pain	1.0 ± 0.82	1.3 ± 0.92	1.3 ± 0.95
Burning	0.5 ± 0.83	0.7 ± 0.88	0.7 ± 0.88
Itching	0.9 ± 0.91	0.9 ± 0.94	0.9 ± 0.93
Ankle circumference in cm (mean, SD)			
Left Leg	24.0 ± 2.11	24.0 ± 2.24	24.3 ± 2.53
Right Leg	23.9 ± 2.07	24.0 ± 2.20	24.2 ± 2.51
Lower leg circumference in cm (mean, SD)			
Left Leg	37.4 ± 3.54	37.6 ± 3.63	37.8 ± 3.82
Right Leg	37.0 ± 3.59	37.3 ± 3.59	37.5 ± 3.83

Tolerability

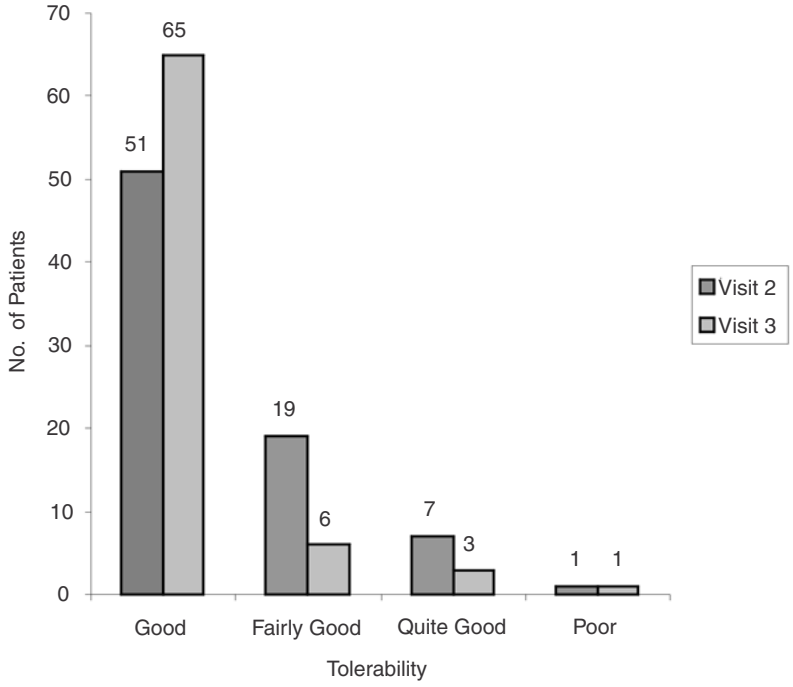
Overall, both the patients' and researchers' perception of tolerability was good (Figure 1). Patients judged the tolerability of the study medication in the majority of the cases at visits 2 and 3 (90 and 95%, respectively) to be 'good' or 'fairly good.' Researchers also judged the tolerability of the study medication in the majority of the cases at visit 2 and 3 (90 and 92%, respectively) to be 'good' or 'fairly good.' Only 2 patients rated the tolerability of the test medication at the end of the study as poor.

Efficacy

Symptom Score

As can be seen in Table 2, the differences in the median values between baseline and visit 3 for each of the symptoms investigated: heavi-

FIGURE 1. Patients' perception of tolerability over the treatment period for the safety population.



ness or tension, pain, burning, and itching and paraesthesias were statistically significant. At baseline, the symptoms were in the range of mild to moderate in nature. By the end of the observation period, the symptoms had almost disappeared. These findings were true for both the PP and ITT populations.

Ankle/Lower Leg Circumference

Both ankle and lower leg circumferences decreased, although the difference in the median value between baseline and visit 3 was generally not statistically significant for both PP and ITT populations. The median and mean values of the ankle circumferences showed a trend towards reduction, which was not clearly seen in the lower leg circumferences.

TABLE 2. Symptom score of the ITT population. The symptoms were rated as 0 = none, 1 = mild, 2 = moderate, 3 = severe.

		Heaviness/ tension	Pain	Burning	Itching/ paraesthesias
Visit 1	Mean (SD)	1.7 (0.79)	1.3 (0.92)	0.7 (0.88)	0.9 (0.94)
	Median	2.0	1.0	0.0	1.0
	Min-Max	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0
Visit 3	Mean (SD)	0.8 (0.88)	0.4 (0.67)	0.2 (0.56)	0.3 (0.67)
	Median	1.0	0.0	0.0	0.0
	Min-Max	0.0-3.0	0.0-3.0	0.0-3.0	0.0-3.0
	Median Difference	1.0	1.0	0.0	1.0
	P-value*	<0.001	<0.001	<0.01	<0.001

*Wilcoxon signed rank test.

Photoplethysmography

The PPG technique showed no convincing results. Generally, the analysis of the data generated from the PPG technique for all patient groups was not significant. However, the validity of this data is questionable.

During the study, we found that the PPG parameters could vary greatly in the same patient between visits. The variations were mostly too large to be explained by clinical or physiological reasons. Validation measurements made after the trial in three healthy volunteers showed that the method had an internal error of about 30%. We therefore regard the PPG data generated during the study to be invalid measures of any changes in the state of CVI and believe that the data should not be considered.

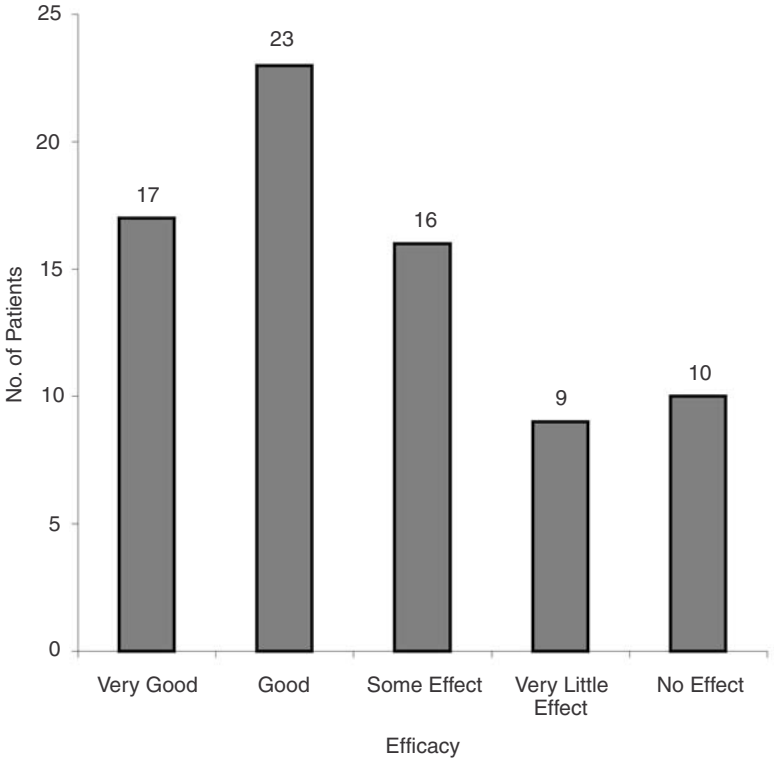
General Assessments of Efficacy

General assessments of efficacy were good from patients and researchers. The majority of patients in both the PP and ITT (Figure 2) populations (49 and 51%, respectively) rated the efficacy to be ‘good’ or ‘very good’ at visit 3 and only 10 patients (13%) claimed to have experienced no effect by the end of the study.

Assessments of efficacy improved from visit 2 to visit 3 in both the PP and ITT populations, indicating that a longer time period is favourable.

When asked the question “Would you (the patient) use the Aesculaforce tablets again?” 81% of patients said yes.

FIGURE 2. Patients' general assessment of efficacy at visit 3 for the ITT population.



Study drug compliance was high, with over 60 patients having a compliance rate of equal to or greater than 75%.

DISCUSSION

Aesculaforce is a fresh plant extract made from seeds of the horse chestnut tree, *Aesculus hippocastanum*. It is the active ingredient of two existing Aesculus-preparations currently on the market: a gel and a lower dosed tablet (standardized to 20 mg aescin to be taken 3 × 2 tablets daily). Two clinical trials have previously been carried out with this extract: one with the gel[10] and one with the tablet.[11] Both treatments

were efficacious regarding reduction of the symptom score as well as the ankle circumference. Both were well tolerated and safe.

The aim of this study was to assess, primarily, the safety of newly developed enteric coated tablets (Aesculaforce 50 mg), standardised to 50 mg aescin, in the treatment of mild to moderate forms of CVI. Efficacy was explored as a secondary parameter.

In this trial, the different patient populations were comparable with regard to age, symptom score and ankle and lower leg circumference at baseline. Study drug compliance was high, with over 60 patients having a compliance rate of equal to or greater than 75%.

With regards to safety, only 4 adverse events were rated as probably related to the study drug and 2 patients judged the tolerability of the test medication at the end of the study as poor. The majority of adverse events reported were mild in nature and transient.

Recently, two meta-analyses on the efficacy and safety of Aesculus preparations in the treatment of CVI have been published.[12,13] Siebert et al. analysed 18 randomised controlled trials (RCTs), which involved a total of 1,051 patients, and 3 observational studies (10,725 patients). Pittler et al. analysed 14 clinical trials (nine placebo-controlled, four reference-controlled and one against compression stockings), which involved a total of 1,213 patients. Pittler et al. found an adverse event rate of 14.4% when taking Aesculus preparations and Siebert et al. reported a rate ranging from 1-36%, based on the trials reporting any side effect at all. The most frequent events reported were mild gastrointestinal disorders. In comparison to the results of these meta-analyses, Aesculaforce 50 mg tablets are as safe and well tolerated as other Aesculus preparations.

Since this was an open clinical trial it was generally difficult to assess the extent to which the treatment was efficacious. However, for each of the symptoms investigated the difference in the median value between baseline and visit 3 was found to be statistically significant, in both the PP and ITT populations. These results are in accordance with the findings of the two meta-analyses discussed above where pain, leg fatigue and itching also improved, even though it was not always statistically significant. Both ankle and lower leg circumferences decreased, although the difference in the median value between baseline and visit 3 was not statistically significant, in both the PP and ITT populations. The PPG technique showed no convincing results. Validation measurements made after the trial in three healthy volunteers showed that the chosen method was not precise enough and had an internal error of around 30%. We therefore regard the PPG data generated during the

study to be invalid and believe the data should not be considered. Finally, general assessments of efficacy were good from patients and researchers. The majority of patients in both the PP and ITT populations (49 and 51%, respectively) rated the efficacy to be 'very good' or 'good' at visit 3 and only 10 patients (13%) claimed to have experienced no effect by the end of the study. The efficacy results suggest that Aesculaforce 50 mg tablets are effective in the treatment of mild to moderate CVI.

CONCLUSION

Aesculaforce 50 mg tablets were well tolerated and mainly mild or moderate adverse events were experienced over a treatment period of 8 weeks in patients with Widmer stage I or II CVI. Subjective assessments of symptoms and efficacy continued to improve between visit 2 to visit 3 as well as from visit 1 to visit 2, indicating that a longer treatment and assessment period is favourable. The statistically significant improvement of the symptom scores indicates that after a treatment period of 8 weeks, patients with CVI benefit from reduced signs and symptoms. This conclusion is supported by both the researcher's and patient's assessment of efficacy, who rated the treatment to be 'good' or 'very good' in the majority of the cases and by the fact that when asked the question "Would you (the patient) use the Aesculaforce tablets again?" 81% of patients said yes. The results of this study indicate that Aesculaforce 50 mg tablets are a safe, well-tolerated and efficacious treatment for Widmer stage I and II CVI.

REFERENCES

1. Angle N & Bergan JJ (1997) Chronic venous ulcer. British Medical Journal 314 (1019).

2. Bosanquet N (1992) Costs of venous ulcers: From maintenance therapy to investment programmes. Phlebology (1), pp. 44-46.

3. Mills S & Bone K (2000) Principles and Practice of Phytotherapy. Churchill Livingstone.

4. Alexander MF, Fawcett JN & Runciman PJ (1994) Nursing Practice: Hospital and Home. Churchill Livingston.

5. Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JD, Martin JB, Kasper DL, Hauser SL & Longo DL (1998) Harrison's Principles of Internal Medicine. McGraw-Hill 14th Edition, Volume 2.

6. Ernst E (2001) The Desktop Guide To Complementary and Alternative Medicine, an Evidence-Based Approach. Harcourt Publishers Limited.

7. ESCOP (1999) European scientific cooperative of phytotherapy. Monograph on medicinal uses of plant drugs.

8. Schultz-Ehrenburg U & Blazek V (2001) Value of quantitative photoplethysmography for functional vascular diagnostics. Skin Pharmacology and Applied Skin Physiology 14, pp. 316-323.

9. Marston WA (2002) PPG, APG, Duplex: Which non-invasive tests are most appropriate for the management of patients with chronic venous insufficiency? Seminars in Vascular Surgery 15 (1), pp. 13-20.

10. Shah D, Bommer S & Degenring FH (1997) Aesculaforce® in chronic venous insufficiency. Schweiz. Zschr. GanzheitsMedizin.

11. Geissbuehler S & Degenring FH (1999) Treatment of chronic venous insufficiency with Aesculaforce® Vein Gel. Schweiz. Zschr. GanzheitsMedizin 11, pp. 82-87.

12. Siebert U, Brach M, Srocyzynski G & Uberla K (2002) Efficacy, routine effectiveness and safety of horsechestnut seed extract in the treatment of chronic venous insufficiency, International Angiology 21 (4), pp. 305-315.

13. Pittler MH & Ernst E (2003) Horse chestnut seed extract for chronic venous insufficiency (Cochrane Review) in: The Cochrane Library (1), Oxford: Update Software. pp. 1-18.