

# Micronised Purified Flavonoid Fraction

## A Review of its Use in Chronic Venous Insufficiency, Venous Ulcers and Haemorrhoids

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#### Data Selection

**Sources:** Medical literature published in any language since 1980 on micronised purified flavonoid fraction, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

**Search strategy:** Medline search terms were 'diosmin hesperidin' or 'micronised purified flavonoid fraction'. EMBASE search terms were 'diosmin hesperidin' or 'micronised purified flavonoid fraction'. AdisBase search terms were 'diosmin hesperidin' or 'micronised purified flavonoid fraction'. Searches were last updated 2 December 2002.

**Selection:** Studies in patients with chronic venous insufficiency, venous ulcers or haemorrhoids who received micronised purified flavonoid fraction. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

**Index terms:** Micronised purified flavonoid fraction, diosmin hesperidin, chronic venous insufficiency, venous ulcers, haemorrhoids, pharmacodynamics, pharmacokinetics, therapeutic use.

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## Summary

### Abstract

Micronised purified flavonoid fraction (MPFF) [Daflon<sup>®</sup> 500mg<sup>1</sup>], an oral phlebotropic drug consisting of 90% micronised diosmin and 10% flavonoids expressed as hesperidin, improves venous tone and lymphatic drainage, and reduces capillary hyperpermeability by protecting the microcirculation from inflammatory processes. The absorption of diosmin is improved by its micronisation to particles with a diameter <2µm.

Compared with placebo, MPFF 500mg twice daily significantly decreased ankle or calf circumference, and improved many symptoms of chronic venous insufficiency (CVI) and plethysmographic parameters in two randomised, double-blind, 2-month studies. Improvement in symptoms was paralleled by an improvement in health-related quality of life in a nonblind, 6-month trial.

Significantly more venous leg ulcers ≤10cm in diameter completely healed with MPFF 500mg twice daily plus standard management (compression and local treatment) for 2–6 months than with standard management alone or with placebo in a nonblind and a double-blind trial. The addition of MPFF to standard management was cost effective in a retrospective pharmaco-economic analysis of the 6-month trial.

Compared with placebo, the duration and/or intensity of individual symptoms of grade 1 or 2 acute internal haemorrhoids improved significantly with 3 tablets of MPFF 500mg twice daily for 4 days then 2 tablets of MPFF 500mg twice daily for 3 days. Two tablets of MPFF 500mg daily for 60 or 83 days reduced the frequency, duration and/or severity of acute haemorrhoidal symptoms and improved the overall signs and symptoms of chronic (recurrent) haemorrhoids com-

<sup>1</sup> Also registered as Ardiun<sup>®</sup>, Alvenor<sup>®</sup>, Arvenum<sup>®</sup> 500, Capiven<sup>®</sup>, Detralex<sup>®</sup>, Elatec<sup>®</sup>, Flebotropin<sup>®</sup>, Variton<sup>®</sup>, Venitol<sup>®</sup>; use of tradenames is for product identification purposes only and does not imply endorsement.

pared with placebo. Compared with a control group, MPFF significantly reduced the risk of secondary bleeding after elective haemorrhoidectomy.

In clinical trials, MPFF had a tolerability profile similar to that of placebo; the most frequently reported adverse events were gastrointestinal and autonomic in nature.

In conclusion, MPFF is a well established and well tolerated treatment option in patients with CVI, venous ulcers, or acute or chronic internal haemorrhoids. MPFF is indicated as a first-line treatment of oedema and the symptoms of CVI in patients in any stage of the disease. In more advanced disease stages, MPFF may be used in conjunction with sclerotherapy, surgery and/or compression therapy, or as an alternative treatment when surgery is not indicated or is unfeasible. The healing of venous ulcers  $\leq 10$  cm in diameter is accelerated by the addition of MPFF to standard venous ulcer management. MPFF may reduce the frequency, duration and/or intensity of symptoms of grade 1 or 2 acute internal haemorrhoids, and also the severity of the signs and symptoms of chronic haemorrhoids.

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### Pharmacodynamic Properties

MPFF, an oral phlebotropic and vascular protective agent consisting of 90% micronised diosmin and 10% flavonoids expressed as hesperidin, increases venous tone, improves lymphatic drainage and reduces capillary hyperpermeability. By reducing the expression of some endothelial adhesion molecules, MPFF inhibits the activation, migration and adhesion of leukocytes, which leads to a reduction in the release of inflammatory mediators and thereby a reduction in capillary hyperpermeability.

Two tablets of MPFF 500mg daily reduced venous distensibility and capacitance, and improved venous tone in patients with various types of venous insufficiency.

Several indices of inflammation in the microcirculation are reduced by MPFF. Plasma levels of some markers of endothelial activation (intercellular adhesion molecule-1 and vascular cell adhesion molecule) and surface expression of some leukocyte adhesion molecules (monocyte or neutrophil CD62L) were significantly reduced from baseline with 2 tablets of MPFF 500mg daily for 60 days in patients with CVI. Capillary hyperpermeability decreased with 2 or 3 tablets of MPFF 500mg daily resulting in a decrease in oedema in patients in two trials.

Daily administration of 1–4 tablets of MPFF 500mg for 1–3 months had beneficial effects on venous oximetry measurements (e.g. increases from baseline in oxygen pressure, oxygen saturation or pH, and decreases from baseline in carbon dioxide pressure) in patients with mild to moderate CVI in two studies. In patients with CVI, 2 tablets of MPFF 500mg daily for 4 weeks increased red blood cell velocity in capillaries; however, relative capillary packed cell volume also increased.

In patients with severe CVI, 2 tablets of MPFF 500mg daily for 28 days decreased intralymphatic pressure and the diameter of lymphatic capillaries and increased the number of functional lymphatic capillaries compared with baseline values.

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### Pharmacokinetic Properties

Most information on the pharmacokinetics of oral MPFF relates to the diosmin portion of the drug. Diosmin is rapidly transformed in the intestine by intestinal flora and absorbed as its aglycone, diosmetin; the unchanged form of diosmin does not appear to be absorbed. Approximately half of an oral 500mg dose of radiolabelled MPFF was absorbed within 48 hours of administration in healthy volunteers. Micronisation of diosmin increased oral absorption compared with

nonmicronised diosmin (57.9 vs 32.7% of a radiolabelled dose was absorbed 0–168 hours postdose). Diosmetin has a rapid distribution period followed by a slower elimination period. Animal studies have demonstrated that radiolabelled diosmetin and/or its metabolites are widely distributed throughout the body.

Diosmetin is rapidly and extensively degraded to phenolic acids or their glycine conjugate derivatives, which are eliminated in the urine; unmetabolised diosmin and diosmetin are not excreted in the urine. The predominant metabolite, 3-hydroxy-phenylpropionic acid, is mainly eliminated in its conjugated form. Unidentified metabolites may be responsible for the pharmacological activity of diosmin.

Approximately half of a radiolabelled dose of diosmin was eliminated in the faeces as unchanged diosmin and diosmetin. Elimination of micronised diosmin is relatively rapid ( $\approx 34\%$  of the dose excreted in the urine and faeces over the first 24 hours and  $\approx 86\%$  over the first 48 hours). There are no known drug interactions with MPFF.

## Therapeutic Efficacy

**In Patients with Chronic Venous Insufficiency:** Compared with placebo, MPFF 500mg twice daily for 2 months significantly decreased ankle and calf circumferences from baseline in two double-blind trials in 36 and 150 patients; improvements were also seen in the symptoms of CVI (e.g. functional discomfort, nocturnal cramps and sensations of leg heaviness, swelling or heat) and plethysmographic parameters (e.g. venous capacitance, distensibility and emptying time).

The efficacy of 2 tablets of MPFF 500mg daily was maintained in the long-term nonblind treatment (6–12 months) of patients with symptoms of CVI. Patients with or without venous reflux in the large ( $n = 4527$ ) 6-month Reflux Assessment and Quality of Life Improvement with Micronised Flavonoids study showed a significant improvement in CEAP (Clinical signs, Etiology, Anatomical distribution, and Pathophysiological dysfunction) classification. Moreover, both groups of patients also showed a significant improvement in their health-related quality of life, as measured by the Chronic Venous Insufficiency Questionnaire global index scores.

In double-blind, 2-month trials in patients with CVI, 2 tablets of MPFF 500mg daily was more effective than the same nominal dosage of nonmicronised diosmin in improving most of the subjective symptoms and objective parameters of CVI; MPFF 500mg improved the signs and symptoms of CVI regardless of the daily administration schedule (2 tablets in either the morning or the evening, or 1 tablet twice daily).

**Effects on Venous Ulcer Healing:** MPFF 500mg twice daily plus standard management (compression and local therapy) for 2–6 months was more effective than standard management alone or with placebo in the complete healing of venous leg ulcers  $\leq 10$ cm in diameter in a nonblind and a double-blind trial. Venous leg ulcers with a diameter  $\leq 10$ cm were completely healed in 32 or 46.5% of patients receiving 2 tablets of MPFF 500mg daily for 2 or 6 months compared with 13% of patients receiving placebo for 2 months or 27.5% of patients in the control group in the 6-month trial. Ulcers  $> 10$ cm in diameter did not completely heal in either the active-treatment or placebo group during the 2-month trial. Compared with the control group in the longer trial, MPFF reduced mean ulcer area (80 vs 65%) and discomfort related to ulcer (64.8 vs 38.3% of patients); this trial did not include ulcers  $> 10$ cm in diameter.

In a retrospective pharmacoeconomic analysis of the 6-month trial, 2 tablets of MPFF 500mg daily was cost-effective in the treatment of venous ulcers compared with the control group receiving standard venous ulcer treatment. Based on the cost per healed ulcer over 6 months, the cost-effectiveness ratio in the MPFF group was 1026 euros (EUR) compared with EUR1872 in the control group (year of costing 1998).

**In Patients with Haemorrhoids:** In two randomised, double-blind, placebo-controlled trials, MPFF 500mg (3 tablets twice daily for 4 days then 2 tablets twice daily for 3 days) significantly reduced the duration and/or intensity of symptoms of acute internal haemorrhoids (e.g. bleeding, pain, and anal discharge) compared with placebo. After the first few days of treatment, systemic and topical anaesthetics were used less by patients receiving MPFF than patients receiving placebo.

In two double-blind trials, treatment with MPFF 500mg twice daily for 60 or 83 days reduced the frequency, duration and/or severity of acute haemorrhoidal symptoms in patients with chronic symptoms of haemorrhoids compared with placebo. Relapses of bleeding were prevented in 18 or 36% more patients receiving MPFF than those receiving placebo; MPFF also effectively treated the symptoms and signs of chronic haemorrhoids.

In a randomised, nonblind trial, MPFF 500mg (3 tablets twice daily for 5 days, then 2 tablets twice daily for 3 weeks) plus fibre (ispaghula husk) resolved bleeding from nonprolapsed internal haemorrhoids as effectively as with rubber band ligation plus fibre and more rapidly than with fibre alone.

In a noncomparative trial in pregnant women, MPFF 500mg (6 tablets daily for 4 days, then 4 tablets for 3 days) reduced median symptom scores for bleeding, pain, rectal discomfort and rectal exudation from baseline. Maintenance treatment with MPFF 500mg twice daily in the antenatal and 30-day postnatal periods reduced the duration of relapses of symptoms of acute haemorrhoids compared with the patient's history.

The proportion of patients with secondary postoperative bleeding after open pedicular haemorrhoidectomy was less in patients receiving MPFF 500mg (2 tablets three times daily for 3 days then 1 tablet three times daily for 4 days) than in the control group (0.9 vs 6.1%).

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## Tolerability

In clinical trials, MPFF was well tolerated with most reported events being mild and transitory. The adverse events most commonly associated with MPFF are gastrointestinal (e.g. abdominal pain, gastric discomfort, nausea, dyspepsia, vomiting and diarrhoea) or autonomic (e.g. insomnia, drowsiness, vertigo, headache and tiredness) in nature. Combined data from clinical trials in patients with CVI or haemorrhoids indicated that the incidence of adverse events was similar in 2850 patients receiving 2 tablets of MPFF 500mg daily and 225 patients receiving placebo (10 vs 13.9% of patients). Gastrointestinal and autonomic events were reported by 6.9 and 1.7% of patients receiving MPFF. Adverse events were the reason for discontinuation in the trials of 1.1% of MPFF recipients compared with 3.2% of placebo recipients.

The incidence or nature of adverse events was not changed by long-term treatment (1 year) with 2 tablets of MPFF 500mg daily, dosages of MPFF 500mg of up to 6 tablets daily for 7 days, age  $\geq 70$  years or the presence of concomitant diseases (i.e. hypertension, atherosclerosis, diabetes mellitus, neurological/psy-

chiatric disease or alcoholism). Two tablets of MPFF 500mg daily for 1 year did not modify blood pressure or laboratory parameters.

## Dosage and Administration

MPFF is available as 500mg tablets and is administered orally. Prescribing information for MPFF may differ between the more than 100 countries (including 9 countries in the EU and 20 other European countries) that have approved its use. In general, MPFF is indicated for the treatment of organic or idiopathic CVI of the lower limbs with symptoms of heavy legs, pain or nocturnal cramps, acute haemorrhoidal attacks or chronic haemorrhoids. In CVI, the recommended dosage is 2 tablets daily (as a single dose in the morning or evening or 1 tablet twice daily); in acute haemorrhoidal attacks, 2 tablets three times daily for 4 days followed by 2 tablets twice daily for 3 days; and in chronic haemorrhoids, 2 tablets daily. MPFF does not interact with any drugs. Caution is recommended when administering MPFF to patients who are breast feeding.

## 1. Introduction

Chronic venous insufficiency (CVI), the deficient return of venous blood flow in the lower limbs, is a widespread disorder that involves either the superficial venous system or both the deep and superficial systems.<sup>[1-4]</sup> Characteristics of CVI include signs (e.g. telangiectases, varicose veins, oedema, skin changes or venous ulcers) or subjective symptoms (e.g. aching, nocturnal cramps or the sensation of heat, burning, tingling, heaviness or tiredness in the legs) related to venous stasis resulting from venous hypertension.<sup>[1,2]</sup>

Venous hypertension develops from venous reflux and/or vein obstruction and is most commonly caused by abnormalities in the venous wall or valves, or by changes resulting from a previous venous thrombosis.<sup>[1]</sup> The causes and symptoms of CVI involve not only structural and functional abnormalities of the veins but also of the skin microcirculation.<sup>[1,2]</sup> Varicose veins, which may develop from the abnormal distensibility of connective tissue in the vein wall, are the most common manifestation of CVI;<sup>[1]</sup> however, some patients may have functional CVI associated with a venular pathology, but no clinical evidence of varicose veins.<sup>[5]</sup> Infiltration of inflammatory cells (macrophages) into the venous wall and leaflets is associated with leukocyte activation<sup>[6,7]</sup> and expression of membrane adhesion proteins.<sup>[8]</sup> Skin changes (e.g. venous eczema, skin pigmentation) and ultimately venous ulcers may occur as a result of im-

pairment in the microcirculation.<sup>[1]</sup> Venous ulcers usually involve a loss of skin with a well defined margin and have a base covered with a yellow exudate; the surrounding skin is erythematous, hyperpigmented or liposclerotic.<sup>[2]</sup> They are often painful and may take a long time to heal. Indeed, most ulcers (50–75%) take 4–6 months to heal and 20% continue to be open at 2 years.<sup>[2]</sup>

Numerous risk factors for varicose veins have been suggested, including lifestyle factors (e.g. occupations that involve prolonged standing<sup>[9]</sup> or sitting<sup>[10]</sup>) or a family history of varicose veins.<sup>[2,4]</sup> The development of varicose veins in patients already susceptible to the condition may be accentuated by obesity or pregnancy.<sup>[2,4,9]</sup> The risk of venous ulcer is directly related to the degree and pattern of venous insufficiency,<sup>[11,12]</sup> and may also be associated with a history of venous thrombosis.<sup>[13]</sup>

The severity of CVI may be assessed by the Clinical signs, Etiology, Anatomical distribution, and Pathophysiological dysfunction (CEAP) classification system.<sup>[14]</sup> The clinical signs of CEAP are divided into the following classes.

- C0: no visible or palpable signs of venous disease.
- C1: telangiectases, reticular veins and malleolar flare.
- C2: varicose veins.
- C3: oedema without skin changes.
- C4: skin changes ascribed to venous disease

(e.g. pigmentation, venous eczema and lipodermatosclerosis).

- C5: as C4 with healed ulceration.
- C6: as C4 with active ulceration.<sup>[14]</sup>

Because of its high prevalence, cost of investigation and treatment, and associated loss of working days, CVI is associated with a substantial socioeconomic cost.<sup>[1,2,4,12]</sup> Medical care costs of CVI accounted for 1–3% of the total annual health care budgets in European countries,<sup>[4,15,16]</sup> and the annual direct plus indirect costs of CVI are approximately one billion US dollars for each of Germany, France and the UK.<sup>[1,2]</sup> CVI was ranked as the 14th most frequent cause of temporary absence from work and the 32nd most frequent cause of retirement due to disability in Brazil.<sup>[17]</sup> Venous ulcers incur the highest cost per patient of all the clinical presentations of CVI because of its chronic nature and high prevalence in the population.<sup>[4]</sup>

Estimates of the prevalence of varicose veins and venous ulcers vary considerably and depend on the definition of the condition and methodology of assessment.<sup>[4,9,12]</sup> According to population-based epidemiological studies in various countries,<sup>[9]</sup> 25–32% of woman and 7–40% of men have varicose veins. In the Framingham study, the incidence per year of varicose veins was 2.6% in women and 1.9% in men.<sup>[18]</sup> The prevalence of open or open plus healed venous ulceration is  $\approx 0.3$ <sup>[9]</sup> and  $\approx 1$ %.<sup>[9,19]</sup> Women have a prevalence of venous ulcers that is approximately two to three times greater than in men.<sup>[9]</sup> The prevalence of both varicose veins and venous ulceration increases consistently with age.<sup>[2,4,9,12]</sup>

Haemorrhoids result from the distal displacement of the anal cushions and are a very common and widespread condition.<sup>[20,21]</sup> They are classified as either external or internal depending on their origin (i.e. below or above the dentate line) and both types may thrombose.<sup>[22]</sup> External haemorrhoids are painful; internal haemorrhoids may cause rectal bleeding and/or discomfort. Symptoms are chronic with recurrent self-resolving acute episodes.<sup>[23]</sup> The treatment of haemorrhoids depends on the origin and grade of the lesion.<sup>[22]</sup>

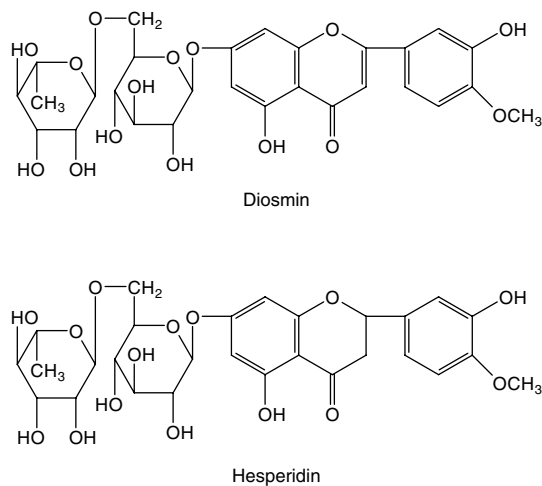
Internal haemorrhoids are graded into the following categories by the extent of prolapse (the extent to which the haemorrhoid descends into the anal canal and out of the anus).<sup>[22]</sup>

- Grade 1: haemorrhoidal tissue is present and identifiable and the main symptom is bleeding.
- Grade 2: haemorrhoids prolapse with a bowel movement but return spontaneously.
- Grade 3: haemorrhoids prolapse and require manual replacement.
- Grade 4: haemorrhoids remain prolapsed despite all efforts at reduction and are often associated with some degree of mucosal prolapse.

Various causes of haemorrhoidal disease have been proposed (e.g. increased maximum resting anal pressure, intrinsic weakness in the blood vessel wall, excessive arterial flow, secondary obstruction of outflow and increased intra-abdominal pressure) but its pathophysiology is not completely understood.<sup>[21,22,24,25]</sup> Haemorrhoids have been associated with many factors including diet, fibre intake, constipation and diarrhoea; however, studies are conflicting in their conclusions on the effect of these factors on the development of haemorrhoidal disease.<sup>[21,24]</sup>

Reports of the prevalence and incidence of haemorrhoids are often anecdotal and are influenced by the definition of haemorrhoids, data collection methods and population of the study.<sup>[21,24]</sup> In a nation-wide questionnaire in the US,<sup>[26]</sup> the prevalence of haemorrhoids was 4.4%; the prevalence was greatest between the ages of 45 and 65 years and there was an equal distribution of haemorrhoidal disease between men and women.

Micronised purified flavonoid fraction (MPFF) [Daflon® 500mg] is a well established oral flavonoid with phlebotropic and venoprotective properties.<sup>[3,27]</sup> It consists of 90% micronised diosmin and 10% flavonoids expressed as hesperidin (which differs from diosmin by the absence of a double bond between two carbon atoms) [figure 1]. Diosmin is synthesised from hesperidin, which is extracted from a type of immature small orange. The micronisation of diosmin to particles with a diameter  $<2\mu\text{m}$  has improved the oral absorption



**Fig. 1.** Chemical structure of diosmin and hesperidin.

of MPFF.<sup>[28]</sup> This article reviews the pharmacological properties and therapeutic efficacy of orally administered MPFF in the management of patients with CVI, venous ulcers or internal haemorrhoids. Although venous ulcers result from CVI (CEAP clinical class C5 and C6), this more severe disease stage is discussed separately from CVI because disease management and clinical trial design in patients with venous ulcers differ from those in patients with CVI.

## 2. Pharmacodynamic Properties

The major pathological event in CVI of the lower limbs is a maintained elevation of venous pressure, which is a consequence of venous reflux, obstruction and/or risk factors of venous disease (e.g. prolonged standing or heat).<sup>[1,12,29,30]</sup> This chronic venous hypertension leads to disturbances of the microcirculation, the site of fluid exchange with interstitial tissues. The activation, migration and adhesion of leukocytes results in a local inflammatory response and is associated with an increase in capillary permeability and fragility,<sup>[30,31]</sup> and parenchymal cell apoptosis.<sup>[32]</sup> The lymphatic system can compensate for the increase in fluid outflow into the surrounding tissues in the early

stages of the disease; if CVI persists or worsens, oedema develops because the lymphatic system becomes overloaded and can no longer handle the excess fluids.<sup>[30]</sup> Free radicals and other cytotoxic substances released by the inflammatory response may in turn lead to trophic changes that may ultimately culminate in the development of venous ulcers;<sup>[29]</sup> however, the precise sequence of events that leads to venous ulceration is not yet clear.<sup>[33]</sup>

The pathogenesis of haemorrhoids may involve the stagnation and stasis of blood in the vascular plexuses of the anal cushions.<sup>[34]</sup> Venous stasis may lead to inflammation resulting in the increased permeability, fragility and necrosis of the vessel wall in the anal cushion and result in bleeding.

MPFF, a phlebotropic and vascular protective agent, increases venous tone, improves lymphatic drainage and protects the microcirculation from inflammatory processes and apoptosis.<sup>[3,27,28,35]</sup> By reducing the expression of some endothelial adhesion molecules,<sup>[36-39]</sup> MPFF inhibits the activation, migration and adhesion of leukocytes at the capillary level.<sup>[32,39-43]</sup> This leads to a reduction in the release of inflammatory mediators such as oxygen-free radicals, prostaglandins and thromboxane,<sup>[44-46]</sup> resulting in a decrease in capillary hyperpermeability.<sup>[35,41,47-49]</sup> An overview of the pharmacodynamic properties of MPFF *in vitro* and in animals is presented in table I. Data on the pharmacodynamic properties of oral MPFF in various patient groups (e.g. patients with CVI, oedema or abnormal capillary fragility) are reviewed in sections 2.1–2.3. The pharmacodynamic properties of MPFF in patients with haemorrhoids have not been examined.

### 2.1 Effect on Venous Tone

By increasing venous tone and thereby reducing venous capacitance, distensibility and stasis, MPFF reduced the venous hyperpressure present in patients with CVI.<sup>[58,59]</sup> Compared with placebo, MPFF significantly improved venous haemodynamics in three double-blind, placebo-controlled, crossover trials in patients with various types of venous insufficiency (reported together in one pa-



**Table I.** Overview of the pharmacodynamic properties of micronised purified flavonoid fraction (MPFF) *in vitro* and in animals**Venous tone**

Prolongs the vasoconstrictor effect of noradrenaline (norepinephrine) on the vessel wall and reduces blood venous stasis *in vitro*<sup>[50]</sup>  
 Increases mechanical tension on bovine metacarpal vein rings *in vitro*<sup>[51]</sup>  
 Increases Ca<sup>2+</sup> sensitivity of the contractile apparatus in rat isolated femoral vein *in vitro*<sup>[52]</sup>  
 Inhibits increases in red blood cell, haematocrit and plasma protein concentrations elicited by the upright position in dogs<sup>[53]</sup>

**Microcirculation**

Inhibits intercellular adhesion molecule-1 expression in ischaemia/reperfusion skeletal muscle injury in rats<sup>[39]</sup>  
 Inhibits leukocyte adhesion and/or migration after ischaemia/reperfusion injury in hamster skin fold<sup>[40-42]</sup> or rat skeletal muscle,<sup>[39]</sup> oxidant challenge in hamster cheek pouch<sup>[43]</sup> and venular mesenteric occlusion/reperfusion in rats<sup>[32]</sup>  
 Inhibits oxygenated free radical production in zymosan-stimulated human neutrophils<sup>[45]</sup> or mouse macrophages<sup>[46]</sup> *in vitro*  
 Inhibits synthesis of prostaglandin E<sub>2</sub> or F<sub>2 $\alpha$</sub>  and thromboxane B<sub>2</sub> in inflammatory granuloma in rats<sup>[44]</sup>  
 Inhibits the increase in microvascular permeability induced by bradykinin or ischaemia in rat cremaster muscle<sup>[47]</sup> and histamine, bradykinin, leukotriene B<sub>4</sub> ischaemia/reperfusion<sup>[41]</sup> or oxidant challenge in hamster cheek pouch<sup>[48]</sup>  
 Improves microvascular reactivity and functional capillary density after ischaemia/reperfusion in hamster cheek pouch<sup>[54]</sup>  
 Reduced parenchymal cell apoptosis in the mesentery microcirculation and microhaemorrhages into the tissue after venular mesenteric occlusion/reperfusion in rats<sup>[32]</sup>  
 Inhibits platelet functions in rats<sup>[55]</sup>

**Lymphatic drainage**

Increases contractility of sheep mesenteric lymphatic collecting ducts *in vitro*<sup>[56]</sup>  
 Increases the frequency of spontaneous contractions in bovine mesenteric lymphatics *in vitro*<sup>[51]</sup>  
 Improves lymphatic drainage in sheep<sup>[56]</sup> and dogs<sup>[57]</sup>  
 Decreases thigh weight, protein concentration in tissue and fibroblast number in rats with acute leg lymphostasis<sup>[30]</sup>

per).<sup>[58]</sup> The efficacy of MPFF was assessed using mercury strain-gauge venous occlusion plethysmography. The optimal dose effect on venous haemodynamic parameters was obtained with a single-dose of 2 tablets of MPFF 500mg compared with a single dose of 1 or 4 tablets of MPFF 500mg in 18 women with venous insufficiency related to a post-thrombotic syndrome. In ten women without venous pathology, a single dose of 2 tablets of MPFF 500mg significantly improved venous distensibility beginning 1 hour after administration and persisting for a further 4 hours ( $p < 0.05$ ). After treatment with 2 tablets of MPFF 500mg once daily for 1 week, the significant effect on venous distensibility was maintained for 24 hours ( $p < 0.05$ ). A single dose of 2 tablets of MPFF 500mg reduced venous capacitance both in healthy women ( $n = 10$ ) and in women with venous insufficiency related to postphlebotic syndrome ( $n = 10$ ) or pregnancy ( $n = 10$ ).<sup>[58]</sup> Compared with placebo, venous capacitance was significantly reduced

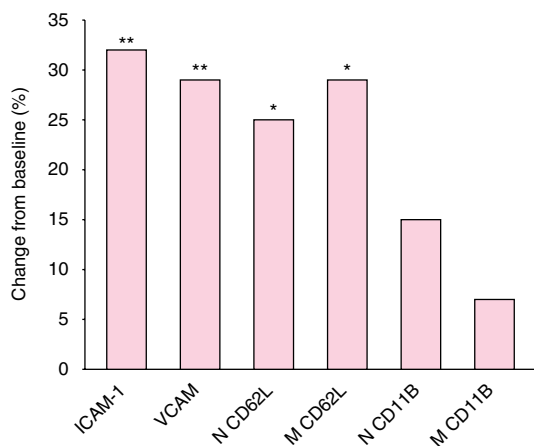
from the first hour after administration ( $p < 0.05$  for each patient group) and persisted for 2 hours ( $p < 0.001$ ).

Venous tone in female volunteers with abnormal venous elasticity and a high risk of developing varicose veins improved with 2 tablets of MPFF 500mg daily for one month in a nonblind, controlled study.<sup>[59]</sup> Volunteers had symptoms of varicose veins and abnormal venous tone but no obvious varicose veins in one leg and symptomatic varicose veins in the opposite leg. Air plethysmography was used to evaluate changes from baseline values in the elastic modulus of veins in the leg without obvious varicose veins. A significant improvement from baseline in the elastic modulus was shown in the 12 volunteers receiving MPFF (increase of  $4.0 \times 10^3 \text{ N/m}^2$ ;  $p < 0.02$ ). In comparison, the elastic modulus did not change significantly from baseline in the 13 volunteers in the control group who received no treatment.

## 2.2 Effect on Microcirculation

### 2.2.1 Leukocyte Activation and Adhesion

MPFF 500mg twice daily for 60 days reduced several indices of inflammation in the microcirculation in 20 patients with CVI in a nonblind study (figure 2).<sup>[36-38]</sup> Plasma levels of some adhesion molecules are elevated in patients with CVI,<sup>[31,60]</sup> and changes in their levels may be feasible markers for response to therapy.<sup>[36,38]</sup> Plasma levels of intercellular adhesion molecule-1 (ICAM-1; binds neutrophils/lymphocytes to endothelial cells) and vascular cell adhesion molecule (VCAM; binds lymphocytes/monocytes to vascular endothelium) decreased significantly from baseline levels ( $p < 0.001$ ; figure 2).<sup>[36]</sup> Moreover, there were significant reductions from baseline ( $p \leq 0.003$ ; figure 2) in the surface expression of some leukocyte adhesion molecules (monocyte or neutrophil CD62L); the decrease in monocyte or neutrophil CD11B expression was not significant.<sup>[38]</sup> These reductions were seen both in patients with CVI with associated dermatological changes (CEAP clinical



**Fig. 2.** Effect of oral micronised purified flavonoid fraction (MPFF) on indices of inflammation in the microcirculation. Changes from baseline values in plasma levels of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule (VCAM) and cell surface fluorescence of monocyte (M) or neutrophil (N) CD62L or CD11B in 20 patients with chronic venous disease receiving MPFF 500mg twice daily for 60 days in a nonblind study.<sup>[36,38]</sup> \*  $p \leq 0.003$ , \*\*  $p < 0.001$  vs baseline.

class C4;  $n = 10$ ) and in patients with less severe disease (C2 or C3;  $n = 10$ ). Significant reductions from baseline in the plasma levels of lactoferrin (36%;  $p < 0.05$ )<sup>[36]</sup> or vascular endothelial growth factor (42%;  $p < 0.02$ )<sup>[37]</sup> were shown only in the C4 patient group.

### 2.2.2 Capillary Permeability and Resistance

MPFF decreased capillary hyperpermeability resulting in a decrease in oedema in two trials.<sup>[35,49]</sup> Increased capillary hyperpermeability is associated with ankle and foot oedema in patients with CVI and leads to skin alteration and eventually ulcerations.<sup>[49]</sup> Capillary hyperpermeability, evaluated using the Landis isotope test with injection of  $\text{Te}^{99\text{m}}$ -albumin, improved significantly ( $p < 0.05$ ) with 2 tablets of MPFF 500mg daily compared with placebo in a randomised, double-blind, placebo-controlled, 6-week trial in 30 patients with idiopathic cyclic oedema.<sup>[35]</sup> Weight loss ( $\geq 1.5$  kg) and a decreased sensation of swelling accompanied this reduction in labelled albumin retention ( $p < 0.05$  vs placebo for each parameter). In a non-blind, 4-week study using strain gauge plethysmography in patients with venous hypertension, MPFF 500mg twice daily ( $n = 21$ ) or 500mg three times daily ( $n = 22$ ) significantly decreased the capillary filtration rate from baseline values in a dose-dependent manner ( $p < 0.05$ ).<sup>[49]</sup>

Compared with placebo, 2 tablets of MPFF 500mg daily improved capillary resistance in patients with abnormal capillary fragility in a randomised, double-blind, 6-week trial.<sup>[61]</sup> At week 6, capillary resistance assessed by the negative suction cup method increased from baseline to a significantly greater extent with MPFF (from 149 to 261mm Hg;  $n = 48$ ) than with placebo (from 151 to 163mm Hg at week 6;  $n = 48$ ) [ $p < 0.001$ ]. Patients receiving MPFF showed a significant improvement in the symptoms of capillary fragility (spontaneous ecchymosis, epistaxis, purpura, petechiae, gingivorrhagia, metrorrhagia and conjunctival haemorrhage) [ $p < 0.001$  vs placebo].

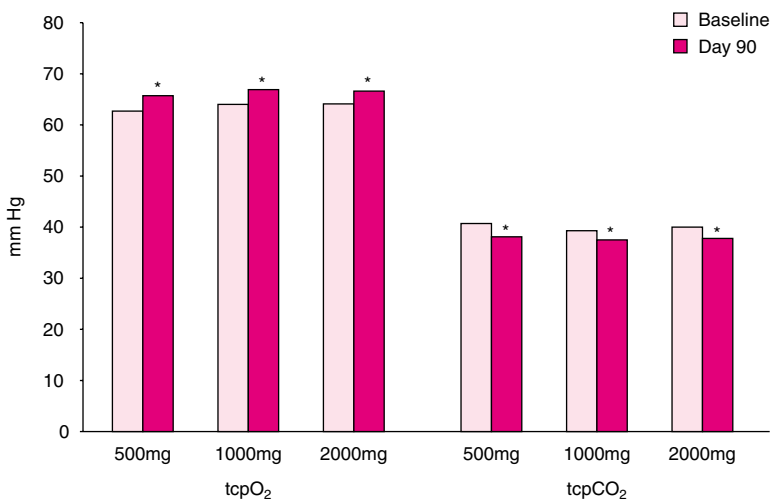
### 2.2.3 Haemorrhological Changes

MPFF had beneficial effects on venous oximetry measurements in patients with mild to mod-

erate CVI in two studies.<sup>[62,63]</sup> During CVI, microcirculatory changes result in regional tissue hypoxia because of maldistribution of blood flow and ischaemic areas.<sup>[63]</sup> Microcirculatory parameters (assessed by transcutaneous oximetry) significantly improved from baseline ( $p < 0.001$ ) with 1, 2 or 4 tablets of MPFF daily for 3 months in 90 evaluable patients with mild CVI in a randomised, double-blind study (figure 3); compression therapy was discontinued before the trial.<sup>[62]</sup> Improvements in these parameters were not significantly different across the three treatment groups.

In a nonblind study in 33 patients with mild or moderate CVI in one leg,<sup>[63]</sup> 2 tablets of MPFF 500mg daily for 30 days significantly increased the partial pressure of oxygen, oxygen saturation and pH and decreased partial carbon dioxide pressure ( $p < 0.01$ ) compared with baseline values (assessed by dorsal pedal venous oximetry measurements). Oximetric data improved to a significantly greater extent in the clinically uninvolved leg than in the involved leg of patients ( $p < 0.05$ ), which may have been a result of lower capillary perfusion pressure in the uninvolved limb.

Two tablets of MPFF 500mg daily improved venous microangiopathy and resolved capillary stasis by increasing red blood cell velocity in capillaries in a nonblind, 4-week study in 24 patients with CVI.<sup>[64]</sup> Decreased red blood cell velocity and increased packed volume are associated with stasis in the microcirculation in the more advanced stages of CVI. Red blood cell velocity increased significantly from baseline to day 28 of treatment ( $p < 0.05$ ) and remained stable for a further 2 weeks without treatment. However, relative capillary packed cell volume increased significantly from baseline to day 28 ( $p = 0.001$ ) and then decreased significantly after treatment was discontinued from day 28 to day 42 ( $p = 0.001$ ). The apparent discrepancy between increased velocity and increased packed cell volume may be accounted for by dissociation between viscosity and velocity at the microcirculatory level (sigma effect) or an improvement in the flexibility of the red blood cells. Other fluorescence capillaroscopic parameters did not change between days 1 and 28 (i.e. maximum intensity and appearance, disappearance or interstitial dwelling time).



**Fig. 3.** Effect of oral micronised purified flavonoid fraction (MPFF) on transcutaneous oximetry parameters. Transcutaneous oxygen (tcpO<sub>2</sub>) and carbon dioxide pressure (tcpCO<sub>2</sub>) at baseline and day 90 of treatment with 1, 2 or 4 tablets of MPFF 500mg daily; results of a randomised, double-blind, 3-month study in 90 evaluable patients with mild chronic venous insufficiency.<sup>[62]</sup> \*  $p < 0.001$  vs baseline.

### 2.3 Effect on Lymphatics

Two tablets of MPFF 500mg daily improved the lymphatic microangiopathy associated with CVI in 24 patients with severe CVI and no active ulceration in a noncomparative study reviewed by Ramelet.<sup>[30]</sup> In patients with advanced stages of CVI, increases in intralymphatic pressure and the diameter and permeability of lymphatic capillaries leads to the transendothelial diffusion of fluids.<sup>[65]</sup> The diameter of lymphatic capillaries and the intralymphatic pressure both decreased significantly ( $p < 0.001$ ) from baseline after 28 days of treatment; the number of functional lymphatic capillaries increased significantly from baseline ( $p < 0.001$ ).<sup>[30]</sup> These improvements may be attributable to an increase in lymphatic flow and drainage, which leads to a reduction in oedema.

### 3. Pharmacokinetic Properties

Available pharmacokinetic data for oral MPFF in humans are very limited (one double-blind study<sup>[28]</sup>) and there are none in special patient groups such as pregnant women or diabetic or elderly patients. Most information on the pharmacokinetics of MPFF relates to the diosmin portion of the drug. Although the absorption characteristics of MPFF are different from those of nonmicronised diosmin, the metabolism of diosmin is similar regardless of the formulation. Therefore, this section also includes some data from a study of the pharmacokinetics of oral nonmicronised diosmin in five healthy volunteers.<sup>[66]</sup> The pharmacokinetic parameters of diosmin in several animal species (including rats, dogs, rabbits and monkeys) have been reported in data from the manufacturer.<sup>[67]</sup>

There are no known drug interactions with MPFF.<sup>[68]</sup>

#### 3.1 Absorption and Distribution

After oral administration, diosmin is rapidly transformed in the intestine by intestinal flora and absorbed as its aglycone, diosmetin.<sup>[66,67]</sup> Plasma samples from humans or animals administered diosmin did not show any traces of diosmin despite

the sensitive assay methods used (i.e. high performance liquid chromatography and gas chromatography linked to mass spectrometry). An *in vitro* study showed that <sup>13</sup>C- and <sup>14</sup>C-diosmin incubated with human gut flora were transformed to diosmetin, luteolin and phenolic acids.<sup>[67]</sup>

Approximately half of an oral 500mg dose of radiolabelled MPFF was absorbed within 48 hours of administration (table II) in a pharmacokinetic study in 12 healthy male volunteers.<sup>[28]</sup> This double-blind, crossover study with a 14-day washout period compared the absorption of radiolabelled MPFF with that of nonmicronised diosmin.<sup>[28]</sup> Because unabsorbed diosmin is not excreted in the urine, absorption was evaluated based on the urinary elimination of radioactivity. Reduction in the particle size of diosmin led to a significant increase in absorption; mean gastrointestinal absorption of micronised <sup>14</sup>C-diosmin was significantly greater than with nonmicronised <sup>14</sup>C-diosmin (57.9 vs 32.7% during 0–168 hours postdose;  $p = 0.0004$ ).<sup>[28]</sup>

Diosmetin had a rapid distribution period followed by a slower elimination period in a single-dose study of nonmicronised diosmin 10 mg/kg in five volunteers.<sup>[66]</sup> The time to the peak plasma concentration of diosmetin was 1 hour and plasma concentrations started to decrease slowly after 2 hours; diosmetin was still detectable after 48 hours. The mean volume of distribution of diosmetin was 62.1L, indicating that there was an

**Table II.** Excretion of micronised purified flavonoid fraction (MPFF) into the urine and faeces. Percentage of the total radioactivity of a single oral 500mg dose of <sup>14</sup>C-MPFF excreted in the urine and faeces in 12 healthy male volunteers.<sup>[28]</sup> Values are expressed as mean values  $\pm$  standard deviation

Time period (hours)	Percentage of total radioactivity	
	urine <sup>a</sup>	faeces <sup>b</sup>
0–24	31.1 $\pm$ 11.1	2.92 $\pm$ 6.56
0–48	49.5 $\pm$ 13.7	36.6 $\pm$ 28.5
0–72	54.4 $\pm$ 18.2	43.8 $\pm$ 30.3
0–168	57.9 $\pm$ 20.2	50.9 $\pm$ 24.2

a Indicates the percentage of the dose that was absorbed from the gastrointestinal tract. Excreted solely as metabolites.

b Indicates the percentage of the dose that was excreted as unchanged (unabsorbed) diosmin and diosmetin.

extensive uptake of the compound by the tissues.<sup>[66]</sup> Animal studies have demonstrated that radiolabelled diosmetin and/or its metabolites are widely distributed throughout the body.<sup>[67]</sup>

### 3.2 Metabolism and Elimination

Diosmetin is rapidly and extensively degraded to phenolic acids or their glycine conjugate derivatives, which are eliminated in the urine.<sup>[66,67]</sup> The predominant metabolite in man is 3-hydroxyphenylpropionic acid which is mainly eliminated in its conjugated form.<sup>[66,67]</sup> Metabolites found in smaller amounts include other phenolic acids corresponding to 3-hydroxy-4-methoxybenzoic acid and 3-methoxy-4-hydroxyphenylacetic acid and 3,4-dihydroxybenzoic acid.<sup>[66]</sup> It is possible that unidentified metabolites may be responsible for the pharmacological activity of diosmin.<sup>[67]</sup>

Elimination of micronised diosmin is relatively rapid with  $\approx 34\%$  of the radiolabelled dose of  $^{14}\text{C}$ -diosmin excreted in the urine and faeces over the first 24 hours and  $\approx 86\%$  over the first 48 hours (table II).<sup>[28]</sup> Unmetabolised diosmin and diosmetin are not excreted in the urine.<sup>[67]</sup> The cumulative excretion of the dose in the urine and faeces was 100% ( $109 \pm 23\%$  0–168 hours).<sup>[28]</sup> Approximately half of the dose was eliminated in the faeces as unchanged diosmin and diosmetin. Unchanged diosmin in the faeces corresponds to unabsorbed diosmin as indicated by the very low biliary excretion of radioactivity in studies of  $^{14}\text{C}$ -diosmin in rats.<sup>[67]</sup>

## 4. Therapeutic Efficacy

The efficacy of oral MPFF in the treatment of patients with CVI (section 4.1), venous ulcers (section 4.2) or acute or chronic (recurrent) internal haemorrhoids (section 4.3) has been evaluated in comparative and noncomparative clinical trials. Unless stated otherwise, patients in each treatment group within each comparative trial were well matched in terms of disease severity and other baseline characteristics, and all data are for intention-to-treat groups.

### 4.1 In Patients with Chronic Venous Insufficiency (CVI)

Randomised, double-blind, 2-month studies have evaluated the effectiveness of MPFF 500mg twice daily in the treatment of functional or objective CVI compared with placebo<sup>[69,70]</sup> or diosmin 900 mg/day.<sup>[71]</sup> Additional details of the results of the placebo-controlled trial by Chassignolle et al.<sup>[69]</sup> have been reported by Tsouderos in a review of three clinical trials of MPFF.<sup>[72]</sup> The effect of various administration regimens of 2 tablets of MPFF 500mg each day has also been examined.<sup>[73]</sup> The long-term efficacy of 2 tablets of MPFF 500mg daily has been studied in two nonblind, multicentre trials of 6- (Reflux Assessment and Quality of Life Improvement with Micronised Flavonoids [RELIEF] study)<sup>[74]</sup> or 12-months' duration.<sup>[75]</sup>

The criteria for patient selection or exclusion varied somewhat in each study. In general, adult patients were eligible for enrolment in the trials if they had clinical symptoms of CVI in the lower legs attributable to primary varicose veins, post-thrombotic syndrome or functional venous insufficiency.<sup>[70,71,73,75]</sup>

Patients were excluded from the trials if they had concomitant active disease,<sup>[74,75]</sup> had other vascular diseases,<sup>[70,71,73,75]</sup> had a history of venous surgery,<sup>[70,71,73,74]</sup> recent deep or superficial venous thrombosis<sup>[71,73]</sup> or recent childbirth.<sup>[70]</sup>

Patients wearing surgical stockings or compression bandages were instructed to continue wearing them;<sup>[70,71,73,74]</sup> in some studies patients must have been using them for more than 2<sup>[71]</sup> or 3 months<sup>[70,73]</sup> prior to inclusion in the trial. There was a higher proportion of women than men enrolled in the studies.<sup>[69-71,73-75]</sup>

The efficacy of MPFF was evaluated by the change in clinical symptoms in the legs, ankle and calf circumferences and/or plethysmographic parameters. The number and type of subjective clinical symptoms (e.g. functional discomfort, sensation of leg heaviness, leg pain, nocturnal cramps, sensation of swelling, paraesthesia, redness and/or cyanosis, sensation of heat and/or burning and

weakness) evaluated in the studies were somewhat different in each study. Patient response was determined by changes in symptom score on a 4-<sup>[69,71,73,74]</sup> or 5-point scale <sup>[75]</sup> where increasing numbers indicated increasing symptom severity. Functional discomfort<sup>[73]</sup> or pain<sup>[74]</sup> were measured on 10-point visual analogue scale in some of the trials. A variety of noninvasive techniques, which correlate with changes in venous pressure, have been developed for objectively quantifying the severity of CVI. These include strain gauge plethysmography (e.g. venous distensibility at various venous occlusion pressures and duration of venous outflow after removal of venous occlusion)<sup>[69,72]</sup> and duplex-ultrasonography (e.g. venous reflux time).<sup>[74]</sup>

In the RELIEF study, changes in CEAP clinical classification were used to assess differences in the severity and in the evolution of symptoms and signs of CVI during MPFF treatment in patients with or without venous reflux.<sup>[74]</sup> In addition, the study used the Chronic Venous Insufficiency Questionnaire (CIVIQ), the first health-related quality-of-life scale specific for CVI, to evaluate the effects of MPFF on health-related quality of life.<sup>[74]</sup> CIVIQ is a 20-question self-administered questionnaire with a range of scores from 0–100 where 100 indicates a very good health-related quality of life.<sup>[76]</sup>

#### 4.1.1 Comparative Trials

##### Comparisons with Placebo

Compared with placebo in two randomised, double-blind, placebo-controlled trials in 36 or

150 patients with CVI, MPFF 500mg twice daily for 2 months significantly decreased ankle or calf circumference,<sup>[69,70,72]</sup> improved many symptoms of CVI (e.g. sensation of heaviness or swelling)<sup>[69,70,72]</sup> (table III) and improved plethysmographic parameters.<sup>[69,72]</sup>

Mean ankle circumference decreased from baseline by 2.2<sup>[72]</sup> and 4.6mm<sup>[70]</sup> at week 4 of MPFF treatment and 4.1<sup>[72]</sup> and 7.1mm<sup>[70]</sup> at week 8 ( $p < 0.001$  vs placebo for both timepoints) in patients with symptoms of CVI. Mean calf measurements also decreased significantly from baseline with MPFF compared with placebo (table III);<sup>[70,72]</sup> reductions of 3.8mm at week 4 ( $p = 0.05$ ) and 5.7mm at week 8 ( $p < 0.001$ ) of MPFF treatment were shown in the trial by Gilly et al.<sup>[70]</sup> There was a significant correlation between the improvements in the symptom score of sensation of swelling and decrease in ankle circumference between the beginning and end of 2 months' treatment with MPFF.<sup>[70]</sup>

Improvements in venous haemodynamics indicated that MPFF increased venous tone in the study by Chassignolle et al. that also evaluated plethysmographic parameters of venous haemodynamics.<sup>[69,72]</sup> MPFF significantly decreased venous capacitance at 50 mm Hg, venous distensibility at 40, 50 and 60mm Hg, total time of venous emptying and the emptying of the final 50% (considered the active phase of venous outflow) compared with placebo ( $p < 0.001$  for all).<sup>[69]</sup>

**Table III.** Efficacy of oral micronised purified flavonoid fraction (MPFF) in patients (pts) with symptoms of chronic venous insufficiency. Summary of the results of three randomised, double-blind, placebo-controlled, 2-month trials in which MPFF 500mg twice daily was compared with twice-daily placebo (PL) or nonmicronised diosmin (DIO) 300mg three times daily.

Reference	Regimen (no. of enrolled/evaluable pts)	Changes in clinical response measures						Decrease in circumference	
		functional discomfort	nocturnal cramps	heat sensation	pain	leg heaviness	swelling sensation	ankle	calf
<b>Comparisons with PL</b>									
Chassignolle et al. <sup>[69]</sup>	MPFF (18) PL (18)	+++		+		+		+++	+++
Gilly et al. <sup>[70]</sup>	MPFF (76) PL (74)	+++	+	+	+	+++	+++	+++	+++
<b>Comparison with DIO</b>									
Cospite, M. et al. <sup>[71]</sup>	MPFF (43) DIO (45)		NS	+	+	+	NS	+++	+++

NS = not significant; +  $p < 0.05$ , ++  $p < 0.01$ , +++  $p < 0.001$  MPFF vs comparator.

#### Comparison with Nonmicronised Diosmin

MPFF 500mg twice daily for 2 months improved most clinical symptoms (table III) and decreased venous outflow parameters to a greater extent than nonmicronised diosmin 300mg three times daily.<sup>[71]</sup> The daily dosage of diosmin, the active principle of MPFF, was equivalent in each arm of the randomised, double-blind, multicentre, 2-month study in 88 evaluable patients. Statistically significant improvements in all subjective symptoms were demonstrated by both treatment groups (*p* values not reported) at the end of 2 months' treatment; however, MPFF was more effective than diosmin for the majority of response measures (table III). Likewise, improvements in objective parameters (ankle or calf circumferences [table III] and plethysmographic measurements) were shown with each treatment but, in general, were greater with MPFF than with the non-micronised formulation.

#### Comparison of Administration Regimens

Two tablets of MPFF 500mg daily for 2 months was effective in improving the signs and symptoms of CVI compared with baseline values, regardless of the daily administration schedule of the drug.<sup>[73]</sup> In a double-blind, multicentre trial in 308 patients with symptoms of CVI, patients were randomised to one of three comparable groups that received 2 tablets of MPFF 500mg in the morning or evening, or MPFF 500mg twice daily. Significant improvements from baseline in functional discomfort were shown by each treatment group during 15–30 days of treatment and continued until the end of treatment (*p* < 0.001); the difference was not significant between the three groups. Leg oedema resolved in 28–43.4% of the 263 patients with leg oedema at baseline (*p* < 0.001).<sup>[73]</sup> Mean ankle and calf circumference measurements of the most affected leg decreased significantly compared with baseline values in each treatment group (*p* < 0.001); patients receiving 2 tablets of MPFF 500mg in the morning had the greatest decrease in mean calf measurements (*p* = 0.025 vs the other treatment groups).

#### 4.1.2 Long-Term Treatment

Two tablets of MPFF 500mg daily maintained its efficacy in the long-term treatment of patients with symptoms of CVI in two nonblind, multicentre trials of 6-<sup>[74]</sup> or 12-months'<sup>[75]</sup> duration.

In the RELIEF trial (*n* = 4527 intention-to-treat population), patients receiving 2 tablets of MPFF 500mg daily showed progressive improvements in the symptoms of CVI, which were paralleled by improvements from more severe (CEAP clinical classes C3 or C4) to less severe (C0–C2) stages of CVI.<sup>[74]</sup> At baseline, the proportion of patients with venous reflux classified as having severe disease was approximately twice as high as the proportion without venous reflux (51.1 vs 25.1%). At the end of 6-months' treatment, 37.7% of patients with venous reflux and 15.7% of patients without venous reflux had severe disease (*p* < 0.001 vs baseline); the proportion of patients with an improvement in CEAP classification was greater in patients with venous reflux than without venous reflux (13 vs 9%; *p* < 0.001). After 6 months, both patient groups in the per-protocol population (*n* = 3174) showed significant improvements from baseline in the study outcome measures (*p* < 0.012; table IV).

In the 1-year trial of 2 tablets of MPFF 500mg daily in 170 evaluable patients, a significant reduction from baseline values in physician-assessed clinical symptoms (functional discomfort, cramps and evening oedema; figure 4), ankle and calf circumference, and patient overall assessment of symptom severity was demonstrated at each 2-month evaluation (*p* < 0.001).<sup>[75]</sup> The rapid reductions observed during the first 2 months of treatment represented approximately 50% of the total improvements ultimately observed after 1 year of treatment; continuing improvements in all parameters, albeit less rapid, were reported at each timepoint from month 2 to month 12.

#### Effect on Health-Related Quality of Life

Improvements in the clinical signs and symptoms of CVI with 2 tablets of MPFF 500mg twice daily were associated with significant improvements in CIVIQ (health-related quality-of-life)

**Table IV.** Efficacy of oral micronised purified flavonoid fraction (MPFF) in patients (pts) with symptoms of chronic venous insufficiency with or without venous reflux. Changes from baseline values after 6 months' treatment with 2 tablets of MPFF 500mg daily in the per protocol population (n = 3174) in the Reflux Assessment and Quality of Life Improvement with Micronised Flavonoids Flavonoids (RELIEF) study<sup>[74]</sup>

	Mean change from baseline		Change from baseline in the % of pts		
	ankle circumference (mm)	pain (points) <sup>a</sup>	leg heaviness	cramps	swelling sensation
Without venous reflux	-11.5*	-2.47***†††	-55.3**	-57.2***††	-48.4***†
With venous reflux	-11.8*	-2.46***	-38.6**	-47.9**	-36.0**

a Measured on a 10-point visual analogue scale where 0 indicates no pain and 10 intolerable pain.

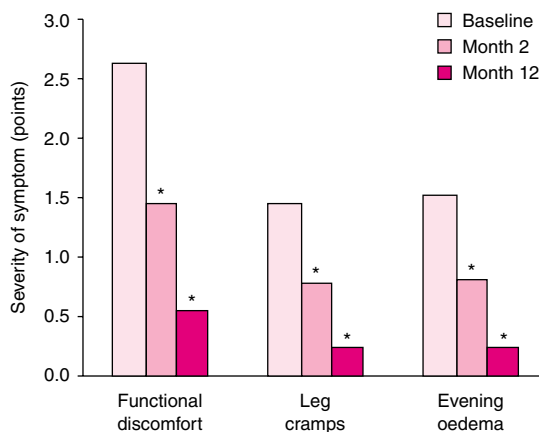
\* p < 0.012, \*\* p = 0.001, \*\*\* p < 0.0001 vs baseline; † p = 0.007, †† p < 0.001, ††† p < 0.0001 vs pts with venous reflux

scores in the RELIEF trial.<sup>[74]</sup> Patients with or without venous reflux showed significant improvement in CIVIQ global index scores (GIS) after 2, 4 and 6 months of treatment (p = 0.0001; figure 5).<sup>[74,77]</sup> GIS increased throughout the study period with the largest improvement occurring during the first 2 months of treatment. In addition, all domains of CIVIQ (psychological, pain, physical dimension and social functioning) improved significantly from baseline at each 2-month timepoint in both patient groups (p = 0.0001). For the domain of pain, patients without venous reflux improved to a greater extent than patients with venous reflux (p = 0.0106 at 6 months).<sup>[74]</sup>

#### 4.2 In Patients with Venous Ulcers

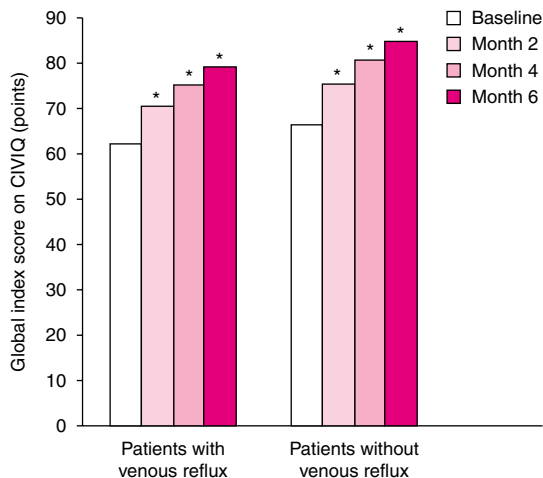
The efficacy of MPFF in augmenting the healing of venous ulcers has been evaluated in a double-blind, placebo-controlled, 2-month trial (n = 105)<sup>[78]</sup> and a nonblind, 6-month trial (n = 140).<sup>[79]</sup> In these randomised, multicentre trials, 2 tablets of MPFF 500mg daily plus standard venous ulcer management was compared with standard venous ulcer management (compression therapy plus local treatment). Patients were included in the trials if they had a venous leg ulcer for a duration of a least 3 months,<sup>[78,79]</sup> a systolic pressure index (ankle/arm) >0.8<sup>[78]</sup> or >0.9.<sup>[79]</sup> The largest ulcer was used as the reference ulcer if multiple ulcers were present.<sup>[78]</sup> In the placebo-controlled study,<sup>[78]</sup> patients were stratified according to ulcer size (≤10 or >10cm) [mean diameter of reference ulcer was 5.5 and 5.3cm in the MPFF and placebo groups]. In the nonblind, 6-month trial,<sup>[79]</sup> ulcers were required have a diameter of 2–10cm; the mean size

of ulcer was larger and a greater proportion of patients had an ulcer exceeding 6cm in diameter in the control group than in the MPFF group (6 vs 5.5cm and 31 vs 43%). Standard venous ulcer management comprised cleaning, compresses, dressings, skin care of the surrounding skin and compression therapy.<sup>[78,79]</sup> The measures of efficacy included the proportion of patients with complete venous ulcer healing (i.e. complete re-epithelisation),<sup>[78,79]</sup> time to complete healing<sup>[78]</sup> and the per-



**Fig. 4.** Improvement in venous symptoms with 2 tablets of oral micronised purified flavonoid fraction (MPFF) 500mg daily. Mean decrease in physician-assessed functional discomfort (sensation of heaviness or heat, paraesthesia or pain in the lower limbs), leg cramps (mostly occurring at night) and evening oedema (oedema or swelling of the feet and/or ankles mostly occurring at the end of the day) from baseline with 2 tablets of MPFF 500mg daily in a noncomparative, multicentre, 12-month trial in 170 evaluable patients with functional symptoms of venous insufficiency.<sup>[75]</sup> Symptoms were assessed on a 4-point scale where 0 indicated symptoms were absent and 4 indicated symptoms were very intense and very frequent. \* p < 0.001 vs baseline.





**Fig. 5.** Improvement in health-related quality-of-life scores with oral micronised purified flavonoid fraction (MPFF). Improvements in the global index score of the Chronic Venous Insufficiency Questionnaire (CIVIQ) with 2 tablets of MPFF 500mg daily for 6 months in 3656 evaluable patients with symptoms of CVI with or without venous reflux in a nonblind, multinational study.<sup>[74,77]</sup> CIVIQ scores range from 0–100 where 100 indicates a very good health-related quality of life. \* p = 0.0001 vs baseline.

centage of ulcer surface area healed.<sup>[78,79]</sup> In addition, the retrospective cost-effectiveness of MPFF in the treatment of venous ulcers in patients with CVI over 6 months was assessed in the nonblind trial.<sup>[79]</sup>

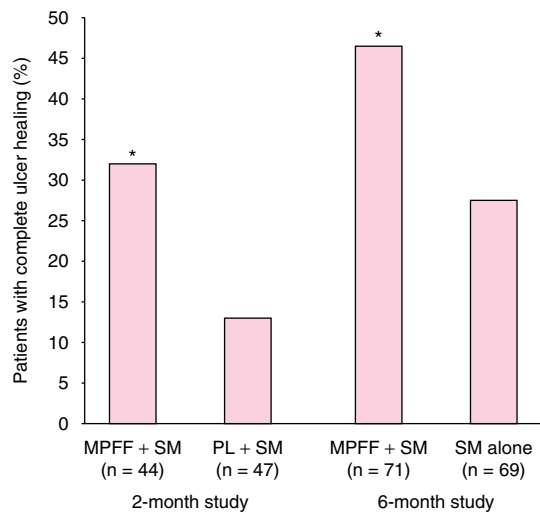
**4.2.1 Effects on Venous Ulcer Healing**

The addition of 2 tablets of MPFF 500mg daily to standard venous ulcer management accelerated the complete healing of venous leg ulcers ≤10cm in diameter (figure 6).<sup>[78,79]</sup> MPFF 500mg twice daily plus standard management completely healed venous ulcers ≤10cm in diameter in 19% more patients than standard management plus placebo or standard management alone in a double-blind, 2-month trial (32 vs 13%; p = 0.028)<sup>[78]</sup> and a nonblind, 6-month trial (46.5 vs 27.5%; p < 0.05).<sup>[79]</sup> Ulcers >10cm in diameter did not completely heal in either the active-treatment or placebo group during the 2-month trial.<sup>[78]</sup> In subgroup analysis by ulcer size in the 6-month trial,<sup>[79]</sup> ulcers measuring between 3 and 6cm in diameter

were completely healed in a significantly greater proportion of patients receiving MPFF plus standard management (n = 35) than in those receiving standard management alone (n = 25) [60 vs 32%; p < 0.05]. Ulcers <3cm diameter were completely healed in 71% of patients receiving MPFF versus 50% of patients in the control group; ulcers >6cm in diameter were completely healed in 9% of MPFF recipients and 13.3% of patients in the control group.<sup>[79]</sup>

Treatment with MPFF for 2 months significantly shortened the time to complete healing of ulcers ≤10cm in diameter relative to placebo (p = 0.037).<sup>[78]</sup> The odds ratio for complete healing with MPFF compared with placebo was similar for patients with diabetes mellitus and without diabetes mellitus (odds ratios 2.5 and 2.23).

In the 2-month trial, a similar change in ulcer surface area was shown by the two treatment groups,<sup>[78]</sup> however, in the longer nonblind trial,<sup>[79]</sup> mean ulcer area was reduced to a significantly



**Fig. 6.** Efficacy of oral micronised purified flavonoid fraction (MPFF) plus standard venous ulcer management (SM) in the complete healing of venous ulcers ≤10cm in diameter. Patients with venous ulcers received SM (compression therapy plus local treatment) plus 2 tablets of MPFF 500mg daily or placebo (PL) in a randomised, double-blind, multicentre, 2-month trial,<sup>[78]</sup> or SM plus 2 tablets of MPFF 500mg daily or SM alone in a randomised, nonblind, multicentre, 6-month trial.<sup>[79]</sup> \*p < 0.05.

greater extent in patients receiving MPFF plus standard management than in patients receiving standard management alone (80 vs 65%;  $p < 0.05$ ). In comparison with standard management alone in the 6-month trial,<sup>[79]</sup> the addition of MPFF to standard management significantly reduced discomfort related to ulcer (64.8 vs 38.3% of patients;  $p < 0.01$ ), but no between-group differences were seen in other secondary clinical symptom endpoints (pain, heavy legs or night cramps).

#### 4.2.2 Cost-Effectiveness

MPFF plus standard venous ulcer management was cost-effective in the treatment of venous ulcers in the nonblind, 6-month study by Gliński et al.<sup>[79]</sup> Based on the cost per healed ulcer over 6 months, the MPFF group had a lower cost-effectiveness ratio than the control group (1026 euros [EUR] vs EUR1872) in a retrospective pharmacoeconomic analysis (year of costing 1998).<sup>[79]</sup> The MPFF group had lower costs per patient over 6 months than the control group; the cost of direct medical care, drugs and dressings, laboratory tests, Doppler examination and home health care was EUR39 lower per patient and the cost of hospitalisation was EUR128 lower per patient. Because there were no statistically differences in the number of adverse events between the two groups, costs for adverse events were not included.<sup>[79]</sup>

#### 4.3 In Patients with Haemorrhoids

Several randomised, double-blind, placebo-controlled trials have evaluated the efficacy of oral MPFF<sup>[23,80,81]</sup> in the management of acute internal haemorrhoids. MPFF plus fibre was compared with fibre alone or fibre plus rubber band ligation in the treatment of bleeding nonprolapsed haemorrhoids in a randomised, nonblind trial.<sup>[82]</sup> A non-comparative trial assessed the use of MPFF in the management of acute haemorrhoids associated with pregnancy in patients with amenorrhoea of >28 weeks and acute haemorrhoidal disease of ≤7 days' duration.<sup>[83]</sup>

Patients included in the trials had a history of haemorrhoidal disease (mainly grade 1 or 2 internal haemorrhoids), which was confirmed by clinical

examination including proctoscopy.<sup>[23,80-83]</sup> In the double-blind, placebo-controlled trials, patients had an acute haemorrhoidal attack with<sup>[81]</sup> or without rectal bleeding<sup>[80]</sup> for less than<sup>[81]</sup> or no more than 3 days,<sup>[80]</sup> or an acute episode of haemorrhoids within the previous 2 months.<sup>[23]</sup> In the second phase of the trial by Misra et al.,<sup>[81]</sup> treatment was continued for an additional 83 days in the patients whose bleeding had ceased by the end of the initial 7-day phase.

Among exclusion criteria in the trials were external thrombosed haemorrhoids,<sup>[23,80]</sup> previous haemorrhoidectomy,<sup>[23]</sup> haemorrhoids requiring surgery,<sup>[23,80,83]</sup> prior laser treatment for haemorrhoids,<sup>[81,83]</sup> recent or current treatment with a phlebotropic, anticoagulant or anti-inflammatory agent.<sup>[23,80,81,83]</sup> In one trial, certain topical or systemic analgesics were permitted.<sup>[80]</sup>

In the treatment of acute symptoms, MPFF 500mg was generally given orally as a loading dosage of 3 tablets twice daily for 4 days then 2 tablets twice daily for 3 days;<sup>[80,81,83]</sup> in long-term treatment, the dosage was 500mg twice daily.<sup>[23,81]</sup>

The efficacy of MPFF in the management of haemorrhoids was evaluated by changes in number, frequency and duration of acute attacks,<sup>[23,81,82]</sup> and/or changes in the objective signs (e.g. swelling, congestion, bleeding, exudation and prolapse) or subjective symptoms (e.g. pain, pruritus, tenesmus and mucous discharge) of haemorrhoids.<sup>[23,80,83]</sup>

A randomised, nonblind trial evaluated the efficacy of MPFF in decreasing the proportion of patients with secondary bleeding after elective haemorrhoidectomy.<sup>[84]</sup> Secondary bleeding, the major complication of this procedure, occurs in 3.3–6.7% of patients ≈7–14 days after surgery.<sup>[84]</sup>

##### 4.3.1 Comparison with Placebo

###### Treatment of Acute Symptoms

Significant improvements in the duration and/or intensity of symptoms of acute internal haemorrhoids were reported with MPFF 500mg (3 tablets twice daily for 4 days then 2 tablets twice daily for 3 days) in two randomised, double-blind, placebo-controlled trials in 100 patients (table V).<sup>[80,81]</sup>

Improvements in the individual symptoms of acute haemorrhoids (bleeding, anal discomfort, pain, anal discharge, proctitis) and overall patient-evaluated symptoms were reported in both patient groups in the trial by Cospite et al.;<sup>[80]</sup> improvements were significantly greater with MPFF than with placebo ( $p \leq 0.006$ ). The greater overall improvement in symptoms with MPFF than with placebo was evident by day 2 of treatment and increased during days 3–7 ( $p < 0.001$  at all timepoints). After the first few days of treatment, MPFF recipients used authorised systemic (glafenine) and topical (lidocaine 5%) analgesics to a significantly lesser extent than placebo recipients ( $p < 0.05$  on day 3 to day 7 of treatment).

#### Treatment of Chronic Symptoms

Long-term treatment with MPFF 500mg twice daily for 60<sup>[23]</sup> or 83 days<sup>[81]</sup> reduced the risk of relapse of acute haemorrhoidal symptoms in two randomised, double-blind, placebo-controlled trials in 120<sup>[23]</sup> and 100 patients<sup>[81]</sup>, respectively, with chronic symptoms of haemorrhoids. Relapses of bleeding occurred in 18 or 36% fewer patients receiving MPFF than placebo ( $p < 0.05$ ) in the 83-day preventative phase of the 3-month trial<sup>[81]</sup> or in the 2-month trial.<sup>[23]</sup> In the 2-month trial, the mean number of relapses per patients and the duration and severity of acute attacks were significantly decreased with MPFF compared with placebo ( $p < 0.01$ ; table VI).<sup>[23]</sup>

Compared with placebo, MPFF 500mg twice daily for 2 months also effectively treated the symptoms and signs of chronic haemorrhoids (table VI).<sup>[23]</sup> After 2 months of treatment, overall

symptom and sign scores as well as scores for individual symptoms (pain, pruritus, bleeding, tenesmus and mucous discharge) and signs (bleeding on examination, oedema and erythema) were significantly less in the MPFF group than in the placebo group ( $p < 0.01$ ).

#### 4.3.2 MPFF plus Fibre in Comparative Trials

Treatment with MPFF plus fibre resolved bleeding from nonprolapsed internal haemorrhoids 64% more rapidly than fibre alone ( $p = 0.03$ ) in a randomised, nonblind trial; the time to resolution was not significantly different between the MPFF plus fibre group and the rubber band ligation plus fibre group (table VII).<sup>[82]</sup> The number of recurrences of bleeding during 3 months of intervention plus 3 months of observation without intervention was not significantly different between any of the three treatment groups (fibre [ispaghula husk 3.5g twice daily for 3 months], fibre plus 3 tablets of MPFF 500mg twice daily for 5 days then 2 tablets twice daily for 3 weeks, or fibre plus rubber band ligation of three internal haemorrhoids).

#### 4.3.3 In Pregnant Patients

Symptoms of acute haemorrhoids in 50 pregnant patients improved with short-term MPFF treatment in a noncomparative trial.<sup>[83]</sup> In the first phase of the trial, patients received 3 tablets of MPFF 500mg twice daily for 4 days, then 2 tablets twice daily for 3 days; in the antenatal and 30-day postnatal periods, patients received MPFF 500mg twice daily. After a median of 4 days in the initial phase, overall haemorrhoidal symptom scores improved from baseline by 66% (95% CI 79.1–52.9).<sup>[83]</sup> After treatment with 2 tablets of MPFF

**Table V.** Efficacy of oral micronised purified flavonoid fraction (MPFF) compared with placebo (PL) in the treatment of acute internal haemorrhoids. Results of two randomised, double-blind studies in which patients with acute bleeding from internal haemorrhoids received 3 tablets of MPFF 500mg twice daily for 4 days then 2 tablets twice daily for 3 days

Reference (no. of pts)	Parameter	MPFF	PL
Cospite et al. <sup>[80]</sup> (100)	Decrease in attack duration <sup>a</sup> (% of pts)	77.5**	24.5
	Decrease in attack intensity <sup>a</sup> (% of pts)	89.8**	38.8
Misra et al. <sup>[81]</sup> (100)	Cessation of bleeding on third day of treatment (% of pts)	80*	38
	Mean duration of bleeding (days)	4.9*	7.0

a Compared with the duration of attacks in the past year.

\*  $p < 0.01$ , \*\*  $p < 0.001$  vs PL.

**Table VI.** Efficacy of long-term oral micronised purified flavonoid fraction (MPFF) 500mg twice daily compared with placebo (PL) in the treatment of internal haemorrhoids. Results of a randomised, double-blind, 2-month study in patients (pts) with an acute attack of internal haemorrhoids during the previous 2 months<sup>[23]</sup>

Regimen (no. of evaluable pts)	Acute relapse				Overall chronic symptom score <sup>a</sup>		Overall chronic sign score <sup>b</sup>	
	pts with at least 1 relapse (%)	mean no. of relapses	duration (days)	severity <sup>c</sup>	baseline	endpoint	baseline	endpoint
MPFF (58)	40*	0.6**	2.6**	1.1**	6.6	1.1**	4.9	0.9**
PL (55)	76	2.1	4.6	1.6	6.1	4.0	4.5	2.9

a The total of scores for pain, pruritus, bleeding, tenesmus and mucous discharge. Each symptom was assessed on a scale of 0 to 3; maximum overall score is 15. A decrease in score is consistent with improvement.

b The total of scores for bleeding on examination, oedema and erythema. Each symptom was assessed on a scale of 0 to 3; maximum overall score is 9. A decrease in score is consistent with improvement.

c On a scale of 1 to 3 where a lower score is consistent with less severity.

\*  $p < 0.05$ , \*\*  $p < 0.01$  vs placebo.

500mg twice daily for a further 3 days, there was a significant reduction from baseline in median symptom scores for bleeding, pain, rectal discomfort and rectal exudation ( $p < 0.05$ ). Although MPFF reduced the proportion of patients with inflammation at proctoscopy by 46% ( $p < 0.001$ ), the proportion of patients with prolapse or thrombosis was not significantly reduced.

In the antenatal period, maintenance treatment with MPFF 500mg twice daily in 44 patients significantly reduced both the frequency and duration of relapses of symptoms of acute haemorrhoids compared with baseline values (history during the current pregnancy and the year preceding it) [ $p <$

0.001].<sup>[83]</sup> During the 30 days of postnatal maintenance treatment ( $n = 41$ ), there was a significant reduction in the duration of relapses ( $p < 0.05$ ).

#### 4.3.4 To Reduce Bleeding After Haemorrhoidectomy

MPFF reduced the risk of secondary bleeding after elective haemorrhoidectomy performed with a standardised diathermy excision method by a single surgeon.<sup>[84]</sup> Of 114 patients receiving 2 tablets of MPFF 500mg three times daily for 3 days then 1 tablet three times daily for 4 days, one (0.9%) patient had secondary haemorrhage compared with seven (6.1%) of 114 patients in the control group ( $p = 0.03$ ) in a randomised, nonblind trial. In the control group, the mean time that bleeding occurred after surgery was 11.3 days (range 6–15 days); the patient in the MPFF group bled 14 days after surgery. Patients in both groups had three haemorrhoids excised without ligation of the pedicles, received routine postoperative pain relief, bulking agents and laxatives, and had similar postoperative hospital stays (mean 2.1 days for all patients).

## 5. Tolerability

MPFF has been well tolerated by patients participating in clinical trials, with most reported events being mild and transitory.<sup>[69-71,73,75,78,80-85]</sup> In an analysis of several comparative and non-comparative clinical trials in 2850 patients with

**Table VII.** Efficacy of oral micronised purified flavonoid fraction (MPFF) plus fibre in the management of haemorrhoidal bleeding. Results of a randomised, nonblind trial in which patients (pts) with bleeding nonprolapsed haemorrhoids received MPFF plus fibre, fibre alone or rubber band ligation (RBL) plus fibre.<sup>[82]</sup>

Treatment	No. of pts	Haemorrhoidal bleeding	
		no. of days to stop (mean)	recurrence <sup>a</sup> (% of pts)
MPFF <sup>b</sup> plus fibre <sup>c</sup>	39	3.9*	5.1
Fibre <sup>c</sup>	66	10.6	12
RBL <sup>d</sup> plus fibre <sup>c</sup>	57	5.6	21

a During 3 months of intervention plus 3 months of observation without intervention.

b Three tablets of MPFF 500mg twice daily for 5 days then 2 tablets twice daily for 3 weeks.

c Ispaghula husk 3.5g twice daily for 3 months.

d RBL of three internal haemorrhoids.

\*  $p = 0.043$  vs fibre.

CVI or haemorrhoids who received 2 tablets of MPFF 500mg daily for 6 weeks to 1 year,<sup>[85]</sup> gastrointestinal adverse events (e.g. abdominal pain, gastric discomfort, epigastric pain, nausea, dyspepsia, vomiting and diarrhoea) in 6.9% of patients and autonomic adverse events (e.g. insomnia, drowsiness, vertigo, headache, tiredness, anxiety, cramps, palpitations and hypotension) in 1.7% of patients were the most frequently reported events. In these trials, the proportion of patients with an adverse event was similar in patients receiving MPFF (10%) to that in 225 patients receiving placebo (13.9%). Adverse events were similar in nature and incidence between these patient groups. The rate of discontinuation because of adverse events (primarily of gastrointestinal origin) were comparable among patients receiving 2 tablets of MPFF 500mg daily or placebo (1.1 vs 3.2%).<sup>[85]</sup>

In this analysis,<sup>[85]</sup> the incidence of adverse events was not significantly different in patients aged  $\geq 70$  years or with concomitant diseases (i.e. hypertension, atherosclerosis, diabetes mellitus, neurological/psychiatric disease or alcoholism) to that in the total population group. In addition, MPFF did not appear to interact with the drugs used to treat these concomitant diseases.

The incidence of adverse events did not increase with long-term treatment with 2 tablets of MPFF 500mg daily. In a 2-month placebo-controlled trial in patients with CVI,<sup>[70]</sup> 12% of 74 MPFF and 16% of 76 placebo recipients experienced adverse events (mostly of a gastrointestinal nature). In comparison, adverse events were documented by 20 of 215 patients (9%) in a 1-year noncomparative trial.<sup>[75]</sup>

Increasing the dosage of MPFF 500mg to 4–6 tablets daily for 7 days did not change the nature or incidence of adverse events.<sup>[80,81,84]</sup> In placebo-controlled trials of MPFF 500mg (6 tablets daily for 4 days then 4 tablets daily for 3 days;  $n = 100$  in each study) in the treatment of acute haemorrhoids (section 4.3.1),<sup>[80,81]</sup> the incidence of adverse events was similar in MPFF and placebo recipients (2–8% vs 0–6%); gastrointestinal adverse

events were the most frequently reported in both groups.

Treatment with MPFF did not modify blood pressure<sup>[70,75,80,81]</sup> or laboratory parameters.<sup>[70,73,75,81]</sup> Systolic or diastolic blood pressure and laboratory values did not change during treatment with 2 tablets of MPFF 500mg daily for 1 year in a clinical trial ( $n = 215$ ) that monitored these parameters every 4 months.<sup>[75]</sup> Laboratory values (e.g. red blood cells, leukocytes, haemoglobin, hepatic enzymes, blood urea, blood glucose and lipids) remained within normal physiological ranges. Although there was a significant decrease in creatinine levels between the beginning and end of treatment (87.7 to 84.0  $\mu\text{mol/L}$ ;  $p < 0.05$ ), these values remained within the normal range.

In a study in 50 pregnant patients with acute haemorrhoids (section 4.3.3),<sup>[83]</sup> nausea or diarrhoea occurred in seven patients and led to the withdrawal from the study of two patients during the initial phase of the trial. There was no significant change in haemodynamic and biochemical parameters during antenatal treatment, and values were within the normal range at the end of the study. The median antenatal maintenance treatment phase was 8 weeks ( $n = 44$ ) and the postnatal maintenance treatment phase was 30 days ( $n = 41$ ). Ultrasonography did not detect any fetal abnormality ( $n = 44$ ); a malformation was detected at birth in one infant (single umbilical artery) and there was one intrauterine death (true knot in cord and cord around the neck). All evaluable infants ( $n = 39$ ) were mature at birth (median maturity 39 weeks) and the median weight of the infants (2.9kg) was normal for the Indian population.

## 6. Dosage and Administration

MPFF is administered orally and is available as 500mg tablets.<sup>[27]</sup> It is generally indicated for the treatment of organic or idiopathic CVI of the lower limbs with symptoms of heavy legs, pain or nocturnal cramps, and acute haemorrhoidal attacks or chronic haemorrhoids.

MPFF is approved for use in over 100 countries including nine countries in the EU (Austria, Bel-

gium, Denmark, France, Greece, Italy, Luxembourg, Portugal and Spain) and 20 other European countries;<sup>[86]</sup> dosage recommendations and approved indications may vary from country to country.<sup>[68]</sup> In general, the recommended dosage of MPFF 500mg in CVI is 2 tablets daily (as a single dose in the morning or evening or 1 tablet twice daily), in acute haemorrhoidal attacks 2 tablets three times daily for 4 days followed by 2 tablets twice daily for 3 days, and in chronic haemorrhoids 2 tablets daily.<sup>[27,87]</sup>

There are no documented drug interactions with MPFF.<sup>[68]</sup> Caution is recommended when administering MPFF to patients who are breast feeding because of the absence of data concerning the diffusion of MPFF into breast milk. No adverse effects have been reported to date when MPFF was administered during pregnancy.

## **7. Place of Micronised Purified Flavonoid Fraction in the Management of CVI, Venous Ulcers and Haemorrhoids**

Phlebotropic agents act on various venous pathophysiological processes that produce the clinical manifestations of CVI, venous ulcers or haemorrhoids (section 2).<sup>[2,4,24,88,89]</sup> Phlebotropics are classified as benzopyrone derivatives (e.g. coumarin and flavonoids such as MPFF and hydroxyethylrutosides), saponins (e.g. escin [horsechestnut extract]), other plant extracts (e.g. bilberry or grape pip extracts) and synthetic substances (e.g. calcium dobesilate).<sup>[4,88,90]</sup>

MPFF is a well established phlebotropic and vasoprotective agent that has been intensively investigated in well designed clinical trials (section 4). It has been shown to increase venous tone (section 2.1), protect the microcirculation from inflammatory processes (section 2.2), and improve lymphatic drainage (section 2.3). Micronisation of the particle size of diosmin to  $<2\mu\text{m}$  improves the oral absorption and bioavailability of diosmin compared with that of nonmicronised diosmin (section 3.1).

MPFF is associated with an incidence of adverse events similar to that seen with placebo; the majority of adverse events are mild and transitory (section 5). The most common adverse events with MPFF are gastrointestinal (6.9% of patients in clinical trials) and autonomic (1.7%). Increasing the length of treatment or the dosage does not appear to change the nature or incidence of adverse events. MPFF does not modify blood pressure or laboratory parameters or interact with concomitant medications. Moreover, MPFF was well tolerated in a noncomparative study in 50 pregnant patients with haemorrhoids. The following sections discuss the standard management and indication for the use of oral MPFF in the treatment of CVI, venous ulcers and acute or chronic internal haemorrhoids.

### 7.1 CVI

In recent guidelines on the treatment of CVI,<sup>[2,90]</sup> the use of phlebotropic agents is indicated to treat oedema and the symptoms of CVI (e.g. oedema, fatigue, nocturnal cramps and heaviness) in any stage of the disease. In the more advanced stages of CVI, phlebotropics are also used in conjunction with sclerotherapy, surgery and/or compression therapy,<sup>[2,88]</sup> or as an alternative treatment when surgery is not indicated or is unfeasible<sup>[2]</sup> or when patients are unwilling or unable to use compression therapy (elastic stockings or compression bandages).<sup>[90]</sup> These recommendations were supported by clinical trials of phlebotropic drugs including MPFF, which has been extensively evaluated for use in patients with CVI (section 4.1).<sup>[2]</sup>

MPFF 500mg twice daily significantly reduces oedema and several of the subjective symptoms of CVI (functional discomfort, pain or sensation of heat/burning, heaviness or swelling) compared with placebo according to data from two randomised, double-blind, placebo-controlled, 2-month trials (section 4.1.1).<sup>[69,70]</sup> Significantly greater decreases in ankle and calf circumferences, and venous distensibility and emptying time are demonstrated with MPFF than with placebo.

MPFF maintains its efficacy in the long-term treatment of CVI as shown in two 6- or 12-month trials of 2 tablets of MPFF 500mg daily (section 4.1.2). In the large 6-month RELIEF trial, the improvement in the symptoms of CVI was paralleled by a significant change in CEAP classification from a more severe to a less severe disease stage in both patients with or without venous reflux ( $p < 0.001$ ).<sup>[74]</sup> Moreover, both groups of patients also showed a significant improvement in their health-related quality of life as measured by the CIVIQ GIS (section 4.1.2). Most of the improvements in symptoms or GIS occurred during the first 2 months of treatment; however, symptoms continued to improve at each timepoint in the long-term trials.

Micronisation of diosmin improved its efficacy compared with the nonmicronised formulation (section 4.1.1). Two tablets of MPFF 500mg daily for 2 months was more effective than the same nominal dosage of nonmicronised diosmin in improving most of the subjective symptoms and objective parameters (ankle and calf circumferences and plethysmographic measures) in patients with CVI. Improvements were shown with each treatment, but generally were significantly greater with MPFF than nonmicronised diosmin ( $p < 0.05$ ).

Although not as extensively studied as MPFF, other phlebotropic agents are also effective in the treatment of oedema and symptoms of CVI.<sup>[2,4,88,90]</sup> Phlebotropic agents that were more effective in the treatment of CVI than placebo in randomised, double-blind, placebo-controlled clinical trials of 3–26 weeks' duration include: butcher's broom (*Ruscus aculeatus*) 72–75 mg/day,<sup>[91]</sup> calcium dobesilate 1500 mg/day,<sup>[92]</sup> escin (horse-chestnut extract) 100–150 mg/day (reviewed by Pittler and Ernst<sup>[93]</sup>) and hydroxyethylrutosides (reviewed by Wadsworth and Faulds<sup>[94]</sup>). According to Ramelet et al.,<sup>[88]</sup> phlebotropics are all generally well tolerated with adverse events occurring in  $\approx 5\%$  of patients. Adverse events include vertigo, headache, and flatulence and are seldom severe; however, hepatitis has been very rarely reported in patients

taking coumarols or benzarone, and skin rashes may occur with tibenoside and naftazone.<sup>[88]</sup>

In patients in the more advanced stages of CVI, MPFF may be used as the first-line treatment for oedema and the symptoms of CVI, as well as in conjunction with compression therapy, sclerotherapy and/or surgery. The function of compression therapy in the treatment of CVI is to control oedema and counteract the effects of venous hypertension.<sup>[1,2,4]</sup> Compression reduces the superficial venous pressure and the leakage of fluid to the microcirculation and improves the venous return by assisting the muscle pump in the lower leg. The individual requirements of the patient and the severity of disease dictate the type and method of compression used.<sup>[2]</sup> Patients should continue to use compression therapy after surgery or sclerotherapy for varicose veins;<sup>[2]</sup> the use of compression stockings for 1 year significantly reduced the postoperative recurrence of varicose veins compared with no compression therapy in a non-blind trial ( $p < 0.01$ ).<sup>[95]</sup>

Sclerotherapy, the injection of a chemical to obliterate varicose veins, is performed with various sclerosing substances at varying concentrations depending on the indication.<sup>[2,4]</sup> Although initially the vein is obliterated in more than 80% of cases, recanalisation and recurrence frequently occur.<sup>[2]</sup> In general, sclerotherapy is not an alternative to surgery and is indicated for a variety of conditions such as telangiectasia, varices 1–3mm in diameter, varices in which surgery is not advisable and varicose veins around an ulcer.

Surgical treatment for CVI depends on the symptoms, pathology and/or complications of the varices.<sup>[2,4]</sup> Although CVI is likely to be progressive, and new varicose veins may eventually appear, the goals of varicose vein surgery are relief of the symptoms and prevention and treatment of complications. Many different types of surgery (e.g. ablative surgery, ligation of saphenofemoral junction, perforator ligation or endovascular surgery) may be performed as indicated for specific conditions.

## 7.2 Venous Ulcers

Venous ulcers are the most severe manifestation of CVI, are slow to heal, have a tendency to recur<sup>[2,96,97]</sup> and are costly to treat.<sup>[4,98]</sup> The goal of treatment is to not only heal the ulcer but to also prevent its recurrence. In addition to macrovascular haemodynamics, venous ulcer formation involves the microcirculation and endothelium; therefore, its treatment should also consider all of these pathophysiological mechanisms.<sup>[2,12]</sup>

According to recent guidelines,<sup>[2,90]</sup> systemic pharmacological treatment targeting one or more of the factors identified in the pathophysiology of venous ulcers (section 2) may be used as an adjunct to standard (compression and local therapy) venous ulcer management. Although the efficacy of supportive pharmacological therapy has been debatable because of methodological limitations in past trials, recent trials of MPFF (section 4.2.1)<sup>[78,79]</sup> in combination with standard management have overcome these limitations<sup>[2]</sup> and fulfil the recommended trial criteria.<sup>[99]</sup>

MPFF 500mg twice daily in combination with standard management accelerates the complete healing of venous leg ulcers according to data from clinical trials (section 4.2.1). The mechanism of action of MPFF on this effect may be attributable to its protective effects on the microcirculation and the decrease in ICAM-1 and VCAM levels resulting in a decrease in leukocyte trapping and activation (section 2.2).<sup>[29]</sup> Venous leg ulcers with a diameter  $\leq 10$ cm were completely healed in significantly more patients receiving 2 tablets of MPFF 500mg daily in combination with standard management for 2 or 6 months than in patients receiving standard management alone or with placebo ( $p < 0.05$ ; section 4.2.1).<sup>[78,79]</sup> In the 6-month trial, MPFF significantly reduced mean ulcer area (80 vs 65%;  $p < 0.05$ ) and discomfort related to ulcer (64.8 vs 38.3%;  $p < 0.01$ ) compared with the control group.<sup>[79]</sup>

Moreover, MPFF is a cost-effective addition to the standard management of venous ulcers according to a retrospective pharmacoeconomic analysis of the 6-month trial (section 4.2.2). The cost-effec-

tiveness ratio (based on the cost per healed ulcer over 6 months) was lower in the MPFF group than in the control group (EUR1026 vs EUR1872; year of costing 1998).<sup>[79]</sup> The costs of direct medical care (e.g. drugs, dressings and home health care) and hospitalisation were both higher in the control group than in the MPFF group.

Other systemic drugs that have been used in the treatment of venous leg ulcers include pentoxifylline, aspirin, profibrinolytic agents (i.e. stanozolol and defibrotide), hydroxyethylrutosides and intravenous prostaglandin E<sub>1</sub>.<sup>[2,90,98]</sup> The Guidelines of the American Venous Forum<sup>[90]</sup> conclude that, of the systemic drugs studied in the treatment of venous ulcers, only MPFF and pentoxifylline have some efficacy and that aspirin, ifetroban, stanozolol, and hydroxyethylrutosides are ineffective in the treatment of venous ulcers.

In two randomised, double-blind, placebo-controlled, 6-month clinical trials ( $n = 129$ <sup>[100]</sup> and  $80$ <sup>[101]</sup>), pentoxifylline plus compression therapy accelerated the healing of venous leg ulcers compared with placebo. The efficacy shown by pentoxifylline probably results from its inhibitory action on the production of pro-inflammatory cytokines.<sup>[100]</sup> Pentoxifylline 400 or 800mg three times daily healed venous ulcers more rapidly than placebo (83, 71 and 100 days, respectively);<sup>[100]</sup> the between-group difference in healing time was significant only for the higher dosage of pentoxifylline ( $p = 0.043$  vs placebo). However, in the other trial,<sup>[101]</sup> pentoxifylline 400mg three times daily healed a significantly greater proportion of venous ulcers than placebo (64 vs 34%;  $p = 0.03$ ). The efficacy of pentoxifylline in healing ulcers has not been compared with that of MPFF.

In a small ( $n = 42$ ), randomised, double-blind, placebo-controlled trial, intravenous prostaglandin E<sub>1</sub> 60  $\mu$ g/day for up to 6 weeks was significantly more effective than placebo in improving ulcer status ( $p < 0.001$ ) and completely healing ulcers (40 vs 9% of patients;  $p$ -value not reported);<sup>[102]</sup> however, its routine use is hampered by its route of administration and acquisition cost.<sup>[78]</sup>



Graduated compression therapy improves the rate of ulcer healing and decreases the rate of recurrence in patients compliant with compression therapy.<sup>[103-105]</sup> The addition of MPFF to compression therapy may accelerate the healing of venous leg ulcers (section 4.2.1). The mechanism of action of compression therapy is not completely known and involves many components.<sup>[105,106]</sup> These include a possible improvement in venous hypertension and microcirculatory haemodynamics and a decrease in the superficial venous pressure, reducing the leakage of fluid and macromolecules, which decreases oedema.<sup>[2,12,105]</sup> High compression is more effective than low compression but cannot be used in the presence of significant arterial disease. Various types of high compression systems (e.g. multilayer bandaging, short stretch bandages and Unna's boot) have not been shown to have clear differences in effectiveness.<sup>[103]</sup> Importantly, elastic compression stockings must be continued to be used following ulcer healing to prevent the recurrence of ulcers;<sup>[105]</sup> patient non-compliance with compression is consistently associated with ulcer persistence or recurrence.<sup>[104,105,107]</sup> In addition, patients should also be advised to maintain their ideal bodyweight, have two to three 30-minute walks on flat ground each day, avoid standing for long periods, occasionally elevate their legs higher than their heart during the day, and sleep with their legs slightly elevated.<sup>[2]</sup>

Venous ulcers may be treated with topical treatments to keep the lesion clean, preserve the micro-environment, protect the lesion from infectious agents and stimulate cell repair.<sup>[2,4,12]</sup> A wide variety of topical treatments (e.g. occlusive or semi-occlusive medications, absorbents, alginates, debriding agents and collagens) are available as pastes, granules, foams or gels; however, their efficacy has seldom been assessed in well controlled clinical trials.<sup>[4]</sup> None of these topical treatments are ideal; the decision of which products to use should take into account the stage of the disease, the presence of dead tissue, exudate or infection, and the condition of the surrounding skin.<sup>[2]</sup> Because of the increased susceptibility to contact der-

matitis with topical antibacterials, systemic antibacterials are generally used in the treatment of bacterially infected ulcers;<sup>[2,12,90]</sup> importantly, systemic antibacterials should not be used in the management of uncomplicated venous ulcer.<sup>[12,90]</sup>

Surgery or sclerotherapy should be considered as a complement to compression therapy with the objective of correcting haemodynamic changes and/or covering the ulcer surface with grafted skin.<sup>[2]</sup> These measures are most effective in patients with ulcers of the superficial venous system.

### 7.3 Haemorrhoids

Medical treatments, such as MPFF and/or dietary fibre, are considered first-line therapy to control internal haemorrhoidal symptoms.<sup>[24,25]</sup> Haemorrhoidal disease is a benign condition and the anal cushions play an important role in faecal continence;<sup>[21]</sup> therefore, the goal of treatment of haemorrhoids is to relieve the symptoms and not to correct the anatomy.<sup>[22,24,25]</sup> Successful treatment requires correct identification of the condition and an understanding of the underlying pathology; many other anorectal conditions have similar symptoms and the terms haemorrhoids and piles have been misused by both laypeople and medical personnel.<sup>[22,25]</sup>

According to a recent guideline,<sup>[24]</sup> MPFF may be used as a short-term treatment for the symptoms (pain, prolapse and/or bleeding) of internal haemorrhoids. MPFF has been studied in the management of internal haemorrhoids because of its phlebotropic activity, protective effect on the capillaries and anti-inflammatory effects (section 2).<sup>[24,80]</sup> The efficacy of MPFF in alleviating acute internal haemorrhoidal attacks and/or preventing further attacks has been studied in several clinical trials (section 4.3).

As shown in data from trials using varying dosages and study lengths, MPFF effectively alleviates the symptoms of acute internal haemorrhoidal attacks (section 4.3.1). MPFF 500mg (6 tablets daily for 4 days then 4 tablets daily for 3 days) reduces the duration and/or intensity of symptoms of acute haemorrhoids (e.g. bleeding, pain and anal

discharge) relative to placebo (section 4.3.1). Moreover, patients receiving MPFF use less systemic and topical anaesthetics after the first few days of treatment than patients receiving placebo. Bleeding from nonprolapsed internal haemorrhoids resolves more quickly with MPFF 500mg (3 tablets twice daily for 5 days, then 2 tablets twice daily for 3 weeks) plus fibre than with fibre alone, but not significantly more rapidly than with rubber band ligation plus fibre (section 4.3.2). In a non-comparative trial in pregnant women (section 4.3.3), MPFF 500mg (6 tablets daily for 4 days, then 4 tablets daily for 3 days) improved the overall symptoms of haemorrhoids from baseline by 66%.

The frequency and duration of relapses of acute internal haemorrhoidal symptoms are reduced with long-term treatment with 2 tablets of MPFF 500mg daily according to data from clinical trials (section 4.3.1 and 4.3.3). Relative to placebo, MPFF prevents relapses of bleeding in 18–36% more patients, reduces the duration and severity of acute attacks, and reduces the signs and symptoms of chronic haemorrhoids (section 4.3.1). Compared with the patient's history during the current pregnancy and the year preceding it, maintenance treatment with MPFF reduces the frequency and duration of relapses of acute haemorrhoids during the antenatal period in pregnant patients (section 4.3.3); in the 30-day postnatal period, maintenance treatment reduces the duration, but not the frequency, of relapses.

Dietary modifications and high fibre bulking agents are also recommended as initial treatments for haemorrhoids.<sup>[22,24,25,108]</sup> These agents promote soft, but formed, regular bowel movements, which may reduce shear forces during defecation. Supplementation with fibre alleviated the symptoms of haemorrhoidal disease compared with a control group<sup>[109]</sup> or placebo<sup>[110]</sup> in clinical trials. Despite the efficacy of dietary fibre in reducing the symptoms, constipation has not been conclusively shown to be a cause of haemorrhoids.<sup>[25]</sup> Although not studied extensively in clinical trials, sitz baths (which may promote the relaxation of the internal

anal sphincter<sup>[111]</sup>) and proper anal hygiene may also help to alleviate symptoms.<sup>[22]</sup>

Although corticosteroids or anaesthetics (e.g. 5% lidocaine) administered topically are widely used to treat the irritation and pruritus associated with haemorrhoids, their efficacy has not been demonstrated in clinical trials.<sup>[22,24]</sup> Prolonged use of topical corticosteroids is potentially harmful and should be advised against.<sup>[24,108]</sup>

Patients who continue to have symptoms of acute internal haemorrhoids while receiving medical treatment may require instrumental or surgical treatment.<sup>[22,24,25,108]</sup> The purpose of the minimally invasive instrumental approaches is to fix the sliding anal tissue back onto the muscle wall by initiating tissue fibrosis;<sup>[25]</sup> the choice of treatment is often determined by the equipment availability and user familiarity.<sup>[22]</sup> The instrumental treatment of grade 1–2 acute internal haemorrhoids includes injections of sclerosing agents, which directly initiate tissue fibrosis, and laser treatment, infrared photocoagulation, cryotherapy or electrocoagulation, which cause tissue destruction leading to scarring and fibrosis.<sup>[22,24,25,108]</sup> Grade 1–3 internal haemorrhoids may be treated with rubber band ligation which removes excess tissue.

Surgical treatment is required in 5–10% of cases of chronic external or internal haemorrhoids.<sup>[24,25,108]</sup> Elective surgical treatment of internal haemorrhoids may be indicated when patients have grade 3 or 4 haemorrhoids, symptomatic haemorrhoids associated with other benign anorectal conditions requiring surgery (e.g. fistula, fissure or stenosis) or continued symptoms despite medical or minimally invasive measures.<sup>[108]</sup>

MPFF reduces the risk of bleeding following elective haemorrhoidectomy according to data from one trial (section 4.3.4). The proportion of patients with secondary postoperative bleeding after open pedicular haemorrhoidectomy was less in patients treated with MPFF 500mg (2 tablets three times daily for 3 days then 1 tablet three times daily for 4 days) than in patients in the control group (0.9 vs 6.1%). The duration of treatment with MPFF (7 days) may not have been long

enough; bleeding occurred day 6–15 after surgery in the control group (mean 11.3 days) and day 14 in the patient with bleeding in the MPFF group.

#### 7.4 Conclusions

In conclusion, MPFF is a well established and well tolerated treatment option for patients with CVI, venous ulcers, or acute or chronic internal haemorrhoids. MPFF is indicated as a first-line treatment of oedema and the symptoms of CVI in patients in any stage of the disease. In more advanced disease stages, MPFF may be used in conjunction with sclerotherapy, surgery and/or compression therapy, or as an alternative treatment when surgery is not indicated or is unfeasible. The healing of venous ulcers  $\leq 10$ cm in diameter is accelerated by the addition of MPFF to standard venous ulcer management (compression therapy and local treatment); the addition of MPFF appears to be cost effective. MPFF may reduce the duration and/or intensity of symptoms of grade 1 or 2 acute internal haemorrhoids. Although the duration of treatment with MPFF for the prevention of relapse of acute internal haemorrhoids remains to be clarified, the frequency of acute symptoms and the severity of the signs and symptoms of chronic haemorrhoids may be reduced with long-term MPFF treatment.

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