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Comparative Analysis of Therapeutic Options for Chronic Venous Insufficiency in Austria and Serbia: Conventional Pharmacotherapy, OTC Products and Dietary Supplements

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Abstract

Chronic venous disease (CVD) is one of the most common vascular disorders and may significantly impair patients' quality of life. Venoactive drugs are widely used in the conservative management of CVD and are recommended by current European clinical guidelines for the treatment of venous symptoms. This thesis provides an overview of venoactive drugs and compares their availability on the pharmaceutical markets of Serbia and Austria, with particular emphasis on the role of the pharmacist in supporting their rational use.

The comparison showed differences in the availability and regulatory status of venoactive products between the two countries. However, the overall therapeutic approach remains based on the same European clinical guidelines. The analysis also confirms the important role of pharmacists in patient counselling, monitoring of therapy, and promoting the rational use of venoactive drugs.

Overall, this thesis demonstrates that, despite differences in product availability and regulatory status, the management of chronic venous disease in Serbia and Austria is based on the same evidence-based therapeutic principles. Together, these findings emphasize the importance of the evidence-based use of venoactive drugs and the role of pharmaceutical care in the management of CVD.

Zusammenfassung

Chronische Venenerkrankungen gehören zu den häufigsten Gefäßerkrankungen und können die Lebensqualität der Betroffenen erheblich beeinträchtigen. Venoaktive Arzneimittel werden häufig in der konservativen Behandlung chronischer Venenerkrankungen eingesetzt und in aktuellen europäischen Leitlinien zur Behandlung venöser Symptome empfohlen. Die vorliegende Masterarbeit gibt einen Überblick über venoaktive Arzneimittel und vergleicht deren Verfügbarkeit auf den pharmazeutischen Märkten Serbiens und Österreichs. Ein weiterer Schwerpunkt liegt auf der Rolle der Apothekerinnen und Apotheker bei der Förderung eines rationalen Einsatzes dieser Arzneimittel.

Die vergleichende Analyse zeigte Unterschiede hinsichtlich der Verfügbarkeit und des regulatorischen Status venoaktiver Produkte in beiden Ländern. Gleichzeitig basiert der therapeutische Ansatz in Serbien und Österreich auf denselben europäischen Leitlinien. Darüber hinaus bestätigt die Analyse die wichtige Rolle der Apothekerinnen und Apotheker bei der Beratung von Patientinnen und Patienten, der Begleitung der Therapie sowie der Förderung eines rationalen Einsatzes venoaktiver Arzneimittel.

Insgesamt zeigt diese Arbeit, dass sich die Behandlung chronischer Venenerkrankungen trotz unterschiedlicher Marktstrukturen und regulatorischer Rahmenbedingungen an denselben evidenzbasierten therapeutischen Grundsätzen orientiert. Die Ergebnisse unterstreichen die Bedeutung eines evidenzbasierten Einsatzes venoaktiver Arzneimittel sowie einer qualitätsgesicherten pharmazeutischen Betreuung.

List of Abbreviations

Abbreviation	Meaning
ALIMS	Medicines and Medical Devices Agency of Serbia
BASG	Austrian Federal Office for Safety in Health Care
CEAP	Clinical, Etiological, Anatomical and Pathophysiological Classification
CVD	Chronic Venous Disease
CVI	Chronic Venous Insufficiency
EMA	European Medicines Agency
ESVS	European Society for Vascular Surgery
EVF	European Venous Forum
MPFF	Micronized Purified Flavonoid Fraction
OTC	Over-the-Counter
UIP	Union Internationale de Phlébologie

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1. Introduction

Chronic venous disease (CVD) is one of the most common vascular disorders and affects a large proportion of the adult population worldwide. Although it is rarely life-threatening, chronic venous disease may progress over time. It can significantly impair patients' quality of life by causing symptoms such as leg pain, heaviness, oedema, and skin changes. Early recognition and appropriate management are important for symptom control and for preventing disease progression.

Venoactive drugs are widely used in the conservative treatment of CVD and are recommended by current European clinical guidelines for the management of venous symptoms. They help reduce symptoms such as leg pain, heaviness, oedema, and cramps, and may improve patients' quality of life. However, pharmacological treatment should not be used as a standalone approach but should be combined with compression therapy and appropriate lifestyle modifications whenever indicated.⁽¹⁾

The principles of treatment are based on the same European clinical guidelines. However, the availability and regulatory status of venoactive products may differ between countries. Comparing the pharmaceutical markets of Serbia and Austria provides an opportunity to identify similarities and differences in the range of available venoactive medicines and related products, as well as in their regulatory classification. Such comparisons provide a better understanding of current therapeutic options and support rational pharmacotherapy in everyday clinical practice.

This thesis provides an overview of venoactive drugs used in the management of CVD and compares their availability on the pharmaceutical markets of Serbia and Austria. It also examines the role of the pharmacist in supporting the rational use of venoactive drugs through patient counselling, monitoring of therapy, and promotion of evidence-based treatment.

2. Definition and Epidemiology of Chronic Venous Insufficiency

Chronic venous insufficiency (CVI) is a vascular disorder resulting from abnormalities of the venous system that impair venous return from the lower extremities. It is generally considered an advanced clinical manifestation of chronic venous disease (CVD), a broad spectrum of disorders affecting the venous system of the lower limbs. Current classifications define CVD as a broad term that includes a wide range of venous disorders, from telangiectasias and reticular veins to varicose veins, oedema, skin changes and venous leg ulceration. CVI, however, refers to the more advanced stages of the disease and mainly corresponds to CEAP classes C3–C6.(1)

The underlying abnormality in CVI is impaired venous return, most commonly caused by venous reflux due to valvular incompetence, venous obstruction, or a combination of both. These alterations may affect the superficial, deep or perforating venous systems. Persistent venous hypertension is the hallmark of disease progression. Over time, it promotes oedema, inflammatory changes, skin damage and, in advanced stages, venous leg ulceration. The underlying pathophysiological mechanisms responsible for these changes are discussed in the following chapter. (1)

The CEAP classification, which categorises chronic venous disorders according to their clinical, aetiological, anatomical and pathophysiological characteristics, is the most widely accepted system for disease classification and reporting. The updated 2020 CEAP classification is recommended for both clinical practice and research, providing a standardised framework for describing disease severity from C0 (no visible or palpable signs of venous disease) to C6 (active venous leg ulcer). (1,2)

Chronic venous disease is highly prevalent worldwide, although reported rates vary considerably because of differences in study design, diagnostic criteria and population characteristics. According to the European Society for Vascular Surgery (ESVS) guidelines, pooled prevalence estimates are approximately 26% for C1 disease, 19% for varicose veins (C2), 8% for oedema (C3), 4% for skin changes (C4), 1% for healed venous ulcers (C5), and 0.4% for active venous ulcers (C6). In Europe, the prevalence of C2 disease has been estimated at approximately 21%. (1)

The prevalence of CVD also increases with age and is influenced by several well-established risk factors, including female sex, obesity, pregnancy, prolonged standing, a sedentary lifestyle and a positive family history. Population ageing, rising obesity rates and increasingly sedentary lifestyles are expected to further increase the burden of CVD and CVI in the coming decades. This is particularly evident in advanced disease, where venous leg ulcers require prolonged treatment and are associated with substantial healthcare costs and a considerable reduction in patients' quality of life.(1,3)

2.1 Pathophysiology of Chronic Venous Insufficiency

Persistent venous hypertension is considered the key pathophysiological mechanism responsible for the development and progression of chronic venous insufficiency. Rather than representing an isolated haemodynamic disturbance, it initiates a cascade of inflammatory and structural changes that progressively impair venous function. Sustained venous hypertension affects the venous wall, venous valves and microcirculation, ultimately leading to the clinical manifestations of the disease.(1,4)

Endothelial dysfunction is one of the earliest consequences of prolonged venous hypertension. Activated endothelial cells promote the adhesion and migration of leukocytes into the venous wall, triggering a chronic inflammatory response. Inflammatory cells release cytokines, chemokines and growth factors that further damage the venous wall and valve structure. As valvular function gradually declines, venous reflux increases, leading to persistently elevated venous pressure and further progression of the disease.(4,5)

Structural remodelling of the venous wall is another characteristic feature of CVI. Alterations in the extracellular matrix, including increased collagen deposition and degradation of elastin, reduce the elasticity and mechanical strength of the venous wall. Matrix metalloproteinases (MMPs), particularly MMP-1, MMP-2, MMP-3, MMP-7 and MMP-9, contribute to extracellular matrix degradation and progressive venous dilatation. Their activity is enhanced by venous hypertension, local hypoxia, oxidative stress and chronic inflammation, further impairing valve function and venous integrity. (4,5)

The inflammatory process also extends to the skin and subcutaneous tissues. Progressive microcirculatory dysfunction increases capillary permeability, resulting in oedema, tissue hypoxia and persistent inflammation. Over time, these changes lead to characteristic skin manifestations, including hyperpigmentation, eczema and lipodermatosclerosis. In advanced stages of the disease, impaired tissue repair and sustained inflammation contribute to the development of venous leg ulcers, the most severe clinical manifestation of chronic venous insufficiency. (1,4)

A better understanding of these pathophysiological mechanisms has supported the development of therapeutic strategies aimed not only at improving venous haemodynamics but also at reducing inflammation, protecting the venous wall and slowing disease progression. This concept forms the basis for many contemporary treatment approaches, including the use of venoactive drugs discussed later in this review. (4)

2.2 Risk Factors for Chronic Venous Insufficiency

The development of chronic venous insufficiency is influenced by a combination of non-modifiable and modifiable risk factors. Although the contribution of individual factors varies among patients, all of them may impair venous circulation, increase venous pressure or promote structural changes within the venous wall, increasing the risk of developing chronic venous insufficiency.(1)

Age is one of the strongest risk factors for CVI, with disease prevalence increasing progressively over time. Female sex is also associated with a higher prevalence of chronic venous disease, largely because of hormonal influences and pregnancy. During pregnancy, hormonal changes, increased blood volume and compression of the pelvic veins contribute to venous hypertension, while the risk of developing CVI increases with each subsequent pregnancy. A positive family history and genetic predisposition further increase susceptibility to the disease, highlighting the importance of inherited alterations affecting the venous wall and connective tissue. (1,6)

Several lifestyle and environmental factors have also been associated with the development of CVI. Obesity, prolonged standing or sitting, physical inactivity and occupations requiring long periods in the same position can impair venous return and reduce the effectiveness of the calf muscle pump.

Smoking and a low-fibre diet have also been identified as contributing factors, although their effects appear to be less pronounced than those of age, obesity and genetic predisposition. Wearing tight clothing or high-heeled shoes has been suggested as a possible contributing factor; however, current evidence indicates that their overall impact is relatively limited. (1,7) Previous deep vein thrombosis, superficial thrombophlebitis and post-thrombotic syndrome are well-established risk factors for the development of chronic venous insufficiency because they may result in persistent venous obstruction or permanent valve damage. In addition, several chronic conditions, including diabetes mellitus, cardiovascular disease and chronic pulmonary disease, may contribute to disease progression by further compromising venous circulation or increasing the overall inflammatory burden. (1)

2.3 Classification of Chronic Venous Insufficiency

The manifestation of chronic venous disease is highly variable, ranging from minor superficial venous changes to advanced skin damage and venous leg ulcers. Because of this variability, a standardized classification system is essential for describing disease severity, facilitating communication between clinicians and supporting research. The most widely accepted system is the **CEAP classification**, which evaluates the disease according to four components: **Clinical (C)**, **Etiological (E)**, **Anatomical (A)** and **Pathophysiological (P)**. Originally introduced in 1994, the classification was updated in 2020 to improve its clinical applicability and reporting standards. (1,2)

In everyday clinical practice, the **Clinical (C)** component is used most frequently because it reflects the visible signs of the disease and allows patients to be classified according to disease severity. Clinical classes range from **C0**, indicating no visible or palpable signs of venous disease, to **C6**, which represents an active venous leg ulcer. Intermediate stages include telangiectasias and reticular veins (C1), varicose veins (C2), oedema (C3), skin changes such as pigmentation, eczema and lipodermatosclerosis (C4), and healed venous ulcers (C5). The 2020 update also introduced recurrent disease subclasses, including C2r for recurrent varicose veins and C6r for recurrent active venous ulcers, as shown in Table 1. (2)

Table 1. Clinical classification of chronic venous disease according to the CEAP classification (based on the 2020 CEAP update)

Clinical class	Clinical findings
C0	No visible or palpable signs of venous disease
C1	Telangiectasias or reticular veins
C2	Varicose veins
C2r	Recurrent varicose veins
C3	Oedema
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C5	Healed venous leg ulcer
C6	Active venous leg ulcer
C6r	Recurrent active venous leg ulcer

Source: Adapted from Lurie et al. (2)

Although the clinical classification is the most familiar part of the CEAP system, a complete assessment also includes the remaining three components. The **Etiological (E)** classification distinguishes congenital, primary and secondary causes of venous disease. The **Anatomical (A)** classification identifies the affected venous segments within the superficial, deep or perforating venous systems, while the **Pathophysiological (P)** classification defines whether the underlying abnormality is caused by venous reflux, venous obstruction or a combination of both. Together, these four components provide a comprehensive description of chronic venous disease and enable a consistent approach to patient assessment in both clinical practice and research. (1,2)

2.4 Symptoms and Clinical Presentation

The clinical presentation of chronic venous insufficiency varies considerably depending on the stage of the disease. While some patients remain asymptomatic for many years, others experience progressive symptoms that gradually interfere with daily activities and quality of life. Clinical manifestations range from mild functional complaints to advanced skin changes and venous leg ulcers, reflecting the progressive nature of the disease. (1)

Early symptoms are often non-specific and include a feeling of heaviness, aching pain, leg fatigue, itching, paraesthesia and nocturnal cramps. Many patients also report a sensation of swelling or tightness in the lower legs, particularly after prolonged standing or sitting. These symptoms typically worsen towards the end of the day and improve with walking, leg elevation or rest, reflecting impaired venous return and reduced efficiency of the calf muscle pump. (1,8)

As the disease progresses, objective clinical signs become more apparent. Varicose veins are the most common visible manifestation and may be accompanied by oedema, skin pigmentation, venous eczema and lipodermatosclerosis. Although many patients with varicose veins seek medical attention primarily because of cosmetic concerns, others develop complications such as superficial thrombophlebitis or bleeding following minor trauma. In advanced stages, chronic venous hypertension and persistent inflammation may lead to venous leg ulceration, representing the most severe manifestation of chronic venous insufficiency. (1,9)

Beyond its physical manifestations, CVI has a substantial impact on patients' quality of life. Persistent symptoms may limit mobility, reduce participation in social and occupational activities and impair work productivity. Disease burden generally increases with clinical severity, and patients with advanced stages of CVI report significantly poorer quality of life than those with milder forms of the condition. (1,4)

2.5 Diagnosis

The diagnosis of chronic venous insufficiency is based on a combination of medical history, clinical examination and imaging studies. A careful assessment of symptoms and clinical signs, together with the CEAP classification, provides the initial evaluation, while imaging techniques are used to confirm the diagnosis and determine the extent of venous disease. (1)

Duplex ultrasound (DUS) is considered the gold standard for the diagnosis of chronic venous insufficiency. This non-invasive technique combines B-mode ultrasound with Doppler assessment, allowing simultaneous evaluation of venous anatomy and blood flow. It enables the identification of venous reflux, venous obstruction and the affected venous segments within the superficial, deep and perforating venous systems. Because of its high diagnostic accuracy, wide availability and non-invasive nature, duplex ultrasound is recommended as the first-line imaging modality in patients with suspected chronic venous disease. (1,10)

Additional diagnostic methods may be used in selected patients when further haemodynamic or anatomical assessment is required. Plethysmography can provide information about overall venous function, although it is used less frequently in routine clinical practice. In patients with suspected proximal venous obstruction, post-thrombotic syndrome or complex venous anatomy, computed tomography venography (CTV) or magnetic resonance venography (MRV) may be performed to obtain more detailed anatomical information. Invasive investigations, including conventional venography and intravascular ultrasound (IVUS), are generally reserved for selected cases and preoperative planning. (1)

3. Aim of the Study

The aim of this master's thesis is to provide a comprehensive overview of the pharmacological management of chronic venous insufficiency (CVI), with particular emphasis on venoactive drugs, and to compare the availability, regulatory status and clinical use of these products in Serbia and Austria.

To achieve this aim, the pharmacological characteristics, mechanisms of action, pharmacokinetic properties and clinical efficacy of the principal venoactive drugs used in the treatment of CVI are reviewed.

The availability of medicinal products, OTC medicines, dietary supplements and topical preparations is also compared between the pharmaceutical markets of Serbia and Austria, with particular attention to differences in regulatory status, commercial availability and therapeutic positioning. In addition, the role of community pharmacists in counselling patients with CVI, promoting the appropriate use of venoactive therapy and supporting treatment adherence is discussed.

4. Therapeutic Approaches to Chronic Venous Insufficiency

The management of CVI aims to relieve symptoms, improve venous function, prevent disease progression and reduce the risk of complications such as skin changes and venous leg ulcers. Because chronic venous insufficiency is a progressive condition with varying clinical manifestations, treatment should be individualized according to disease severity, underlying venous abnormalities and the patient's symptoms. Current clinical guidelines recommend a comprehensive approach that combines conservative measures, compression therapy, pharmacological treatment and interventional procedures when indicated. (1,3)

Early recognition and treatment are essential, as timely intervention may slow disease progression, improve quality of life and reduce the need for more invasive procedures in advanced stages. Management usually begins with conservative measures, while minimally invasive endovenous procedures and surgery are reserved for selected patients, depending on disease severity and clinical presentation. (1,3)

4.1 Lifestyle Modification and Physical Activity

Lifestyle modification is recommended for all patients with CVI regardless of disease stage. Patients are encouraged to adopt measures that improve venous return and reduce venous hypertension. Regular physical activity, weight management and avoidance of prolonged standing or sitting are recommended as part of the initial management in all stages of chronic venous disease. These measures support calf muscle pump function, improve venous circulation and may help reduce symptoms such as leg heaviness, pain and oedema. (1)

Walking, cycling and swimming are among the most frequently recommended forms of exercise because they activate the calf muscles while placing minimal stress on the joints. Regular exercise improves venous return, enhances ankle mobility and contributes to better lower-limb function. Patients are also advised to elevate their legs during periods of rest whenever possible, as this may reduce venous pressure and relieve symptoms. (1,11)

In selected patients, structured physical therapy may provide additional benefit. Exercise programmes focusing on calf muscle strengthening and ankle mobility have been shown to improve calf muscle pump function and functional capacity. Other supportive interventions, including manual lymphatic drainage and intermittent pneumatic compression, may be considered in selected cases, particularly in patients with oedema or reduced mobility, usually in combination with compression therapy. (11,12)

4.2 Compression Therapy

Compression therapy is widely recommended as part of conservative management for patients with chronic venous disease. By applying graduated external pressure to the lower limbs, it improves venous return, reduces venous hypertension and supports the function of the calf muscle pump. As a result, compression therapy helps relieve symptoms such as leg heaviness, pain and oedema, while also reducing venous stasis and improving microcirculation. (1,3)

Medical compression can be achieved using graduated compression stockings or compression bandages. Compression stockings are available in different pressure classes according to the amount of pressure applied at the ankle, with higher compression levels generally recommended for more advanced stages of disease. The choice of compression class depends on the patient's clinical presentation, tolerance and treatment goals.

Table 2. Compression classes and their main clinical indications (based on ESVS 2022 and SVS/AVF/AVLS 2023 clinical practice guidelines)

Compression class	Pressure (mmHg)	Main clinical indications
Class I	18–21	Early chronic venous disease, leg discomfort, pregnancy
Class II	23–32	Varicose veins, oedema, after venous interventions
Class III	34–46	Advanced chronic venous insufficiency, active or healed venous leg ulcers
Class IV	>50	Severe lymphoedema and selected complex cases

Compression therapy plays an important role throughout the course of the disease and is particularly effective in reducing oedema and promoting the healing of venous leg ulcers. Current clinical guidelines recommend high-pressure compression systems for patients with active venous leg ulcers whenever there are no contraindications. Continued use of compression stockings after ulcer healing is also recommended to reduce the risk of ulcer recurrence. (1,3)

Despite its well-established clinical benefits, long-term adherence to compression therapy remains a challenge. Many patients report discomfort, difficulty putting on compression stockings, particularly older adults and individuals with reduced mobility, and dissatisfaction with their appearance. These factors may reduce treatment adherence and, consequently, its effectiveness. For this reason, compression therapy is often combined with other therapeutic approaches, including venoactive drugs, to achieve better symptom control and improve patients' quality of life. (12)

Compression therapy is not suitable for all patients. It is contraindicated in severe peripheral arterial disease, particularly in patients with critical limb ischaemia, and should be used with caution in selected patients with heart failure or other conditions that may limit its safe application. Careful clinical assessment is therefore essential before compression treatment is initiated. (1,12)

4.3 Surgical and Endovenous Treatment

Most patients with chronic venous disease are initially treated with conservative measures. When these are not sufficient to control symptoms or when significant venous reflux is present, interventional treatment may be required. The choice of intervention depends on the patient's clinical presentation, venous anatomy and the underlying cause of venous insufficiency. (1,3)

Traditional surgical treatment includes high ligation, vein stripping and ambulatory phlebectomy. These procedures aim to eliminate venous reflux by removing or disconnecting incompetent veins. Although these procedures remain effective, they have largely been replaced by minimally invasive endovenous techniques because they are associated with shorter recovery time, less postoperative pain and fewer complications. (1,3)

Current clinical guidelines recommend endovenous thermal ablation, including endovenous laser ablation (EVLA) and radiofrequency ablation (RFA), as the preferred treatment for most patients with superficial venous reflux. These techniques close the incompetent vein using heat generated by laser or radiofrequency energy, allowing blood to be redirected through healthy veins. Ultrasound-guided foam sclerotherapy may also be considered in selected patients, depending on the anatomical characteristics of the affected veins and individual treatment goals. In patients with deep venous obstruction or post-thrombotic disease, endovascular procedures such as venous angioplasty and stenting may be indicated. (1,3)

Although interventional procedures effectively correct the underlying anatomical abnormalities, they do not eliminate the chronic nature of the disease. Long-term management therefore often includes continued lifestyle measures, compression therapy and, when appropriate, pharmacological treatment to improve symptom control and reduce the risk of disease progression. (1)

4.4 Venoactive Drugs

Venoactive drugs (VADs) are widely used as part of the conservative management of chronic venous disease. Although they do not correct the underlying anatomical abnormalities responsible for venous reflux or venous obstruction, they may relieve symptoms, improve venous tone, reduce oedema and support microcirculatory function. For this reason, they are commonly prescribed in combination with lifestyle measures and compression therapy, particularly in symptomatic patients. (1,3)

Venoactive drugs include a heterogeneous group of substances of natural, semi-synthetic and synthetic origin. Most of these substances are derived from plant sources, particularly flavonoids and saponins, while others are produced by chemical synthesis or isolated from animal tissues. Despite their different origins, these agents share similar therapeutic goals by targeting several mechanisms involved in the development and progression of chronic venous disease. (4,5)

The pharmacological effects of venoactive drugs are mediated through multiple mechanisms. They improve venous tone, reduce capillary permeability, enhance lymphatic drainage and modulate inflammatory pathways involved in venous hypertension. Some venoactive drugs also reduce leukocyte activation and improve endothelial function.

This helps preserve microvascular integrity and relieve symptoms associated with chronic venous disease. (1,4)

Current European clinical guidelines recommend selected venoactive drugs for the management of venous symptoms, particularly leg pain, heaviness, oedema and cramps. However, the strength of these recommendations varies according to the available clinical evidence for each individual agent. The following sections review the venoactive drugs currently included in clinical guidelines, with particular attention to their mechanism of action, pharmacokinetic properties, clinical use, safety profile and availability in Austria and Serbia. (1,3)

4.4.1 Micronized Purified Flavonoid Fraction (MPFF)

Mechanism of Action

Micronized purified flavonoid fraction (MPFF) is one of the best-studied venoactive drugs used in the management of chronic venous disease. It contains 90% micronized diosmin and 10% other flavonoids, mainly hesperidin, with smaller amounts of diosmetin, linarin and isorhoifolin. The micronization process reduces particle size, which improves gastrointestinal absorption and increases the bioavailability of the active compounds compared with non-micronized formulations. (13,14)

MPFF has several complementary mechanisms of action. At the macrocirculatory level, it increases venous tone by prolonging the vasoconstrictor effect of noradrenaline on the venous wall, leading to reduced venous capacitance and venous stasis. At the microcirculatory level, MPFF decreases capillary permeability, improves lymphatic drainage and limits inflammatory processes associated with CVD. It also reduces leukocyte activation, adhesion and migration, helping to preserve endothelial function and protect the microcirculation. Experimental and clinical studies have additionally demonstrated reduced expression of inflammatory mediators and endothelial adhesion molecules, which may contribute to slowing disease progression. (4,5,15)

Pharmacokinetic Profile

After oral administration, the flavonoid components of MPFF undergo metabolism by the intestinal microbiota, which converts diosmin into its active aglycone, diosmetin. Diosmetin is subsequently absorbed in the small intestine, undergoes extensive phase II metabolism, primarily through glucuronidation, and is eliminated mainly by renal excretion. Micronization significantly improves the absorption of diosmin compared with non-micronized preparations, which is considered one of the main reasons for the superior clinical efficacy of MPFF. Although diosmetin demonstrates affinity for venous tissues, detailed pharmacokinetic data remain limited and differ among available formulations.(13,16,17)

Clinical Efficacy and Guideline Recommendations

MPFF is recommended in current international guidelines as one of the preferred venoactive drugs for symptomatic CVD. Clinical trials and systematic reviews have consistently shown improvements in leg pain, heaviness, oedema, cramps and overall quality of life. Evidence also suggests that MPFF may support healing of venous leg ulcers when used together with compression therapy rather than as a stand-alone treatment. Compared with non-micronized diosmin, MPFF has demonstrated improved clinical efficacy, which is largely attributed to its improved bioavailability following micronization.(1,3,14,18)

Use in Special Populations

Available experimental studies have not demonstrated teratogenic or fetotoxic effects associated with MPFF. However, clinical data in pregnant women remain limited, and its use during pregnancy should only be considered when the expected benefit outweighs the potential risk. Because information regarding excretion into breast milk is insufficient, MPFF is generally not recommended during breastfeeding. Safety and efficacy have not been established in children and adolescents. No dose adjustment is usually required in older adults or in patients with mild renal or hepatic impairment.(19)

Adverse Effects

MPFF is generally well tolerated and has a good safety profile. The most frequently reported adverse effects are mild gastrointestinal symptoms, including nausea, dyspepsia, abdominal discomfort and diarrhoea. Less commonly, patients may experience headache, dizziness or mild skin reactions such as rash, pruritus or urticaria. Serious adverse reactions are rare and treatment discontinuation due to adverse effects is uncommon. (15,19)

Drug Interactions and Contraindications

Clinically significant drug interactions with MPFF have not been consistently demonstrated in routine clinical practice. Although experimental studies suggest that diosmetin may inhibit certain cytochrome P450 isoenzymes *in vitro*, the clinical relevance of these findings remains uncertain. The main contraindication is hypersensitivity to diosmin, hesperidin or any other component of the formulation. (20,21)

4.4.2. Diosmin

Diosmin is a semi-synthetic flavonoid that occurs naturally in small amounts in citrus fruits but is produced commercially by the semi-synthetic modification of hesperidin. It has been used for several decades in the management of CVD because of its venotonic, anti-inflammatory and microvascular protective properties. Unlike MPFF, pure diosmin contains only the isolated active compound and is not micronized, resulting in lower oral bioavailability compared with MPFF. (15,17,22)

Mechanism of Action

The pharmacological effects of diosmin are largely similar to those of MPFF, as diosmin represents its principal active component. Diosmin improves venous tone by enhancing the effect of noradrenaline on the venous wall. This reduces venous distensibility and venous stasis. At the microcirculatory level, diosmin decreases capillary permeability, supports lymphatic drainage and attenuates inflammatory processes within the venous wall. These effects help preserve microvascular function and contribute to the relief of symptoms associated with chronic venous disease.(15,22)

Pharmacokinetic Profile

After oral administration, diosmin is not absorbed in its original form. It is hydrolysed by the intestinal microflora to its active aglycone, diosmetin, which is subsequently absorbed by passive diffusion. Peak plasma concentrations are reached approximately five hours after administration. Diosmetin undergoes extensive hepatic metabolism, primarily through glucuronidation, and is eliminated mainly by renal excretion. The elimination half-life is approximately 8–12 hours. Compared with MPFF, the absence of micronization results in lower oral bioavailability. (17,23)

Clinical Efficacy and Guideline Recommendations

Clinical studies have shown that diosmin may improve symptoms associated with CVD, including leg heaviness, pain, discomfort, oedema and night cramps. However, current clinical guidelines distinguish between pure diosmin and MPFF. Although both belong to the same pharmacological group, the evidence supporting MPFF is stronger because micronization improves bioavailability and most randomized clinical trials have been performed with MPFF rather than isolated diosmin. Consequently, current European guidelines give stronger recommendations for MPFF, particularly in patients with symptomatic chronic venous disease. (1,14)

Use in Special Populations

The available evidence regarding the use of diosmin during pregnancy remains limited. Although animal studies have not demonstrated teratogenic effects, routine use during pregnancy or breastfeeding is not recommended unless the expected benefit outweighs the potential risk. Safety and efficacy have not been established in children. No dose adjustment is generally required in older adults or in patients with mild renal or hepatic impairment. (19)

Adverse Effects

Diosmin is generally well tolerated. The most commonly reported adverse effects are mild gastrointestinal symptoms, including nausea, dyspepsia, diarrhoea and abdominal discomfort. Headache, dizziness and skin reactions such as rash or pruritus occur less frequently and are usually mild and self-limiting. (15,19)

Drug Interactions and Contraindications

No clinically significant drug–drug interactions have been confirmed in routine clinical practice, and diosmin is considered to have a low potential for such interactions. The main contraindication is hypersensitivity to diosmin or to any of the excipients contained in the formulation.(19)

4.4.3 Sulodexide

Sulodexide is a glycosaminoglycan preparation of animal origin, obtained from porcine intestinal mucosa. It consists mainly of a fast-moving heparin fraction (approximately 80%) and dermatan sulphate (approximately 20%). Unlike flavonoid-based venoactive drugs, sulodexide combines venoactive, endothelial-protective and antithrombotic properties, giving it a distinct role in the management of advanced chronic venous disease, particularly in patients with venous leg ulcers.(1,24)

Mechanism of Action

Sulodexide acts through several complementary mechanisms that are relevant to CVD. It helps restore the endothelial glycocalyx, reduces capillary permeability and preserves microvascular integrity. In addition, it exhibits antithrombotic and profibrinolytic activity through interactions with antithrombin III and heparin cofactor II. These effects reduce microvascular inflammation, improve tissue perfusion and may promote wound healing in patients with venous leg ulcers. (24,25)

Pharmacokinetic Profile

Sulodexide is available for both oral and parenteral administration. Following oral administration, it is absorbed from the gastrointestinal tract and demonstrates a high affinity for vascular endothelial tissue. It undergoes hepatic metabolism and is eliminated predominantly by renal excretion. Available pharmacokinetic studies suggest that its therapeutic activity depends not only on circulating plasma concentrations but also on its interaction with the vascular endothelium.(24)

Clinical Efficacy and Guideline Recommendations

Clinical studies have demonstrated that sulodexide improves symptoms associated with chronic venous disease, including oedema, pain, cramps and paraesthesia. Evidence also supports its use in combination with compression therapy in patients with venous leg ulcers, where it may accelerate ulcer healing and improve quality of life. Current European guidelines recognise sulodexide as one of the pharmacological treatment options for selected patients with chronic venous disease, particularly those with advanced disease or venous leg ulcers, although the level of evidence remains lower than that for MPFF.(1,25,26)

Use in Special Populations

Clinical data regarding the use of sulodexide during pregnancy and breastfeeding remain limited. Consequently, its use should be considered only when the expected benefit outweighs the potential risk. Safety and efficacy have not been established in children. In older adults, dose adjustment is generally not required, although treatment should be individualised in patients with an increased bleeding risk or severe renal impairment. (24)

Adverse Effects

Sulodexide is generally well tolerated. The most frequently reported adverse effects are mild gastrointestinal symptoms, including nausea, abdominal discomfort and diarrhoea. Skin reactions such as rash or pruritus occur less commonly and are usually mild and reversible. Owing to its antithrombotic properties, bleeding-related adverse events should be considered, particularly in patients receiving concomitant anticoagulant therapy. (24,25)

Drug Interactions and Contraindications

Sulodexide should be used with caution in patients receiving anticoagulant or antiplatelet therapy because concomitant administration may increase the risk of bleeding. It is contraindicated in patients with hypersensitivity to sulodexide or heparin-like compounds and should be avoided in patients with active bleeding or severe haemorrhagic disorders. (24)

4.4.4 Calcium Dobesilate

Calcium dobesilate is a synthetic venoactive drug that has been used for several decades in the treatment of CVD. Unlike flavonoid-based venoactive drugs, its pharmacological activity is mainly directed at the microcirculation and capillary endothelium. Although clinical studies have demonstrated beneficial effects on symptoms of chronic venous disease, its use is limited by rare but potentially serious haematological adverse reactions. (1,27)

Mechanism of Action

Calcium dobesilate improves microvascular function through several complementary mechanisms. It reduces capillary permeability, protects endothelial cells against oxidative stress and improves capillary resistance. In addition, it inhibits leukocyte adhesion and reduces endothelial dysfunction, which helps limit inflammatory processes associated with

CVD. Calcium dobesilate also has haemorheological effects, including reduced blood viscosity, decreased platelet aggregation and improved erythrocyte deformability. Together, these effects may improve tissue perfusion and reduce oedema. (27,28)

Pharmacokinetic Properties

After oral administration, calcium dobesilate reaches peak plasma concentrations within approximately 5–6 hours. Plasma protein binding is relatively low (20–25%). The drug undergoes limited metabolism and is eliminated predominantly by renal excretion, with an elimination half-life of approximately 5 hours. Approximately 10% of the administered dose is excreted as metabolites, while the remainder is eliminated unchanged in the urine.(28,29)

Clinical Efficacy and Guideline Recommendations

Randomised clinical trials have demonstrated that calcium dobesilate improves several symptoms associated with CVI, including leg pain, heaviness, oedema and nocturnal cramps. However, systematic reviews have reported only modest clinical benefits compared with placebo. Current European guidelines acknowledge its efficacy for symptom relief but assign a lower recommendation grade than MPFF because of limited evidence and concerns regarding safety. (1,27,30)

Use in Special Populations

Clinical data on the use of calcium dobesilate during pregnancy and breastfeeding are limited, and its use should therefore be avoided unless the expected benefit clearly outweighs the potential risk. Safety and efficacy have not been established in children. No dose adjustment is generally required in older adults, although renal function should be considered because renal excretion represents the primary route of elimination. (29)

Adverse Effects

Calcium dobesilate is generally well tolerated. The most commonly reported adverse effects are mild gastrointestinal symptoms, including nausea, diarrhoea and abdominal discomfort. Skin reactions such as rash and pruritus have also been reported. A very rare but clinically important adverse reaction is reversible agranulocytosis, which requires immediate discontinuation of treatment if symptoms suggestive of infection occur.(29,30)

Drug Interactions and Contraindications

No clinically significant drug interactions have been consistently reported. Calcium dobesilate is contraindicated in patients with hypersensitivity to the active substance. Because of the rare risk of agranulocytosis, treatment should be discontinued immediately if patients develop fever, sore throat or other signs of infection until blood counts have been evaluated. (29)

4.4.5. Pycnogenol

Pycnogenol is a standardized extract obtained from the bark of the French maritime pine (*Pinus pinaster*). It contains a mixture of procyanidins, bioflavonoids and phenolic acids, which are considered responsible for its antioxidant and vasoprotective properties. Although Pycnogenol is marketed primarily as a dietary supplement rather than a conventional medicinal product, it has been investigated in several clinical studies involving patients with CVI and other microvascular disorders. (31)

Mechanism of Action

Pycnogenol is thought to improve venous function through several complementary mechanisms. It exhibits antioxidant and anti-inflammatory activity, protects endothelial cells against oxidative stress and reduces capillary permeability. In addition, it may inhibit platelet aggregation, improve endothelial function and support microvascular integrity. Together, these effects may reduce oedema and improve symptoms associated with CVI. (31)

Pharmacokinetic Profile

Pharmacokinetic data on Pycnogenol are limited. After oral administration, its active constituents are absorbed and metabolised before being eliminated from the body. Because it contains several biologically active compounds, its pharmacokinetic profile has not been fully established. (31)

Clinical Efficacy and Guideline Recommendations

Several clinical studies have reported that Pycnogenol may reduce leg heaviness, pain and oedema while improving microcirculatory function in patients with CVI. However, most available studies are relatively small, and the overall quality of evidence remains lower than for established venoactive drugs such as MPFF. Therefore, Pycnogenol is not considered a

first-line pharmacological treatment in current European guidelines but may be used as supportive therapy in selected patients.(1,31,32)

Use in Special Populations

Clinical evidence regarding the use of Pycnogenol during pregnancy and breastfeeding is insufficient; therefore, its routine use in these populations is not recommended. Safety and efficacy have not been established in children and adolescents. (31)

Adverse Effects

Pycnogenol is generally well tolerated when administered at recommended doses. Reported adverse effects are usually mild and include gastrointestinal discomfort, headache and dizziness. Serious adverse reactions have rarely been reported in clinical studies. (31)

Drug Interactions and Contraindications

Because Pycnogenol may influence platelet function, caution is advised when it is used together with anticoagulant or antiplatelet therapy. It should be avoided in patients with known hypersensitivity to *Pinus pinaster* bark extract or any component of the formulation. (31)

4.4.6. Hydroxyethylrutosides (Oxerutins, Troxerutin)

Hydroxyethylrutosides (HRs), also known as oxerutins, are semi-synthetic derivatives of the natural flavonoid rutin. They are produced by hydroxyethylation of rutin to improve its bioavailability and are metabolised to rutin after administration. Troxerutin represents the principal active component of this group and has been used for many years in the treatment of CVI.(33)

Mechanism of Action

HRs primarily act at the level of the microcirculation. They increase capillary resistance, reduce capillary permeability and protect endothelial cells from oxidative stress and leukocyte-induced damage. They also reduce erythrocyte aggregation and improve microcirculatory blood flow, helping to reduce oedema and other symptoms associated with chronic venous insufficiency. (34)

Pharmacokinetic Profile

Following oral administration, HRs are absorbed from the gastrointestinal tract and undergo hepatic metabolism. Elimination occurs mainly via the biliary route, while both the parent compounds and their metabolites are excreted through the liver and kidneys. Troxerutin has an elimination half-life of approximately 18–24 hours, although pharmacokinetic parameters may vary between different formulations. (35)

Clinical Efficacy and Guideline Recommendations

Clinical studies have shown that HRs reduce leg oedema, pain, heaviness and other symptoms of CVI while improving venous haemodynamics and microcirculation. Systematic reviews have confirmed their efficacy and good tolerability, particularly in patients with mild to moderate disease. Nevertheless, current European guidelines consider the level of evidence supporting HRs to be lower than that for MPFF, which remains the preferred pharmacological treatment. (1,34)

Adverse Effects

HRs are generally well tolerated. Reported adverse effects are uncommon and usually mild, consisting mainly of gastrointestinal discomfort, headache, dizziness and occasional hypersensitivity reactions. (34)

Drug Interactions and Contraindications

No clinically significant drug interactions have been consistently reported. HRs should be avoided in patients with known hypersensitivity to the active substance or any component of the formulation. (34)

4.4.7. Other Plant-Derived Venoactive Agents

Several plant-derived compounds have also been investigated for the treatment of CVI. Compared with established venoactive drugs such as MPFF and sulodexide, the available clinical evidence for these agents is generally more limited. Consequently, they are mainly used as complementary therapies or dietary supplements rather than as first-line pharmacological treatment. (36)

Horse chestnut seed extract (*Aesculus hippocastanum* L.), standardized to escin, is one of the best-studied herbal preparations used in CVI. Escin improves venous tone, reduces capillary permeability and may alleviate symptoms such as leg pain, oedema and the sensation of heavy legs. Systematic reviews and current European guidelines support its beneficial effects on symptom relief, although the level of evidence remains lower than that for MPFF. (1,37)

Extracts of *Ruscus aculeatus* L. (butcher's broom) have also demonstrated beneficial effects in patients with CVI. Their pharmacological activity is mainly attributed to steroidal saponins (ruscogenins), which increase venous tone, reduce capillary permeability and exert anti-inflammatory effects. Clinical studies have reported improvements in leg pain, oedema, heaviness and nocturnal cramps, particularly when *Ruscus* extract is combined with hesperidin methyl chalcone and vitamin C. (1,38)

Red vine leaf extract *Vitis vinifera* L. has also been evaluated in randomized clinical trials. Available evidence indicates that it may reduce lower-limb oedema and improve symptoms associated with CVI. However, further high-quality studies are required to confirm its long-term clinical efficacy. (1,39)

Other herbal preparations, including *Centella asiatica* (L.) Urb. (gotu kola), *Ginkgo biloba* L. and various flavonoid combinations, have also been investigated. Although some studies suggest beneficial effects on microcirculation and subjective symptoms, the available evidence remains insufficient to support their routine use as first-line pharmacological therapy in current European guidelines. (1,36)

4.5. Clinical Efficacy of Venoactive Drugs

The clinical efficacy of venoactive drugs has been evaluated in numerous randomized controlled trials and systematic reviews. According to current European guidelines, these agents should be used in combination with compression therapy and lifestyle modification rather than as stand-alone treatments. Their primary role is the relief of symptoms associated with CVI, including leg pain, heaviness, swelling, and nocturnal cramps, as well as improvement of quality of life. In selected patients, some venoactive drugs may also contribute to venous ulcer healing when used in combination with standard wound care and compression therapy.(1,3)

The strength of clinical evidence varies among different venoactive drugs. According to current international guidelines, MPFF has the strongest evidence for relieving symptoms of CVI. It may also improve the healing of venous leg ulcers when used together with

compression therapy and standard wound care. Sulodexide has also demonstrated favourable effects, particularly in patients with advanced chronic venous disease and venous ulceration. Calcium dobesilate and HRs have shown efficacy in reducing oedema and improving several venous symptoms, although the overall quality of evidence is lower. Recent systematic reviews suggest beneficial effects of Pycnogenol, particularly regarding oedema reduction and improvement of microcirculatory parameters; however, additional high-quality studies are required before it can be routinely recommended in clinical guidelines(1,14,36)

Table 3 summarizes the reported efficacy of the principal venoactive drugs for the management of individual symptoms of CVI based on current European guidelines and available systematic reviews

Table 3. Clinical efficacy of venoactive drugs in the management of CVI

Venoactive drug	Venous pain	Heavy legs	Feeling of swelling	Ankle oedema	Venous ulcer healing*
MPFF	+++	+++	+++	+++	+++
Sulodexide	+++	++	++	+++	++
Calcium dobesilate	++	++	++	++	+
HRs	++	++	++++	++	+
Pycnogenol	++	++		++	Insufficient evidence

+++ strong evidence; ++ moderate evidence; + limited evidence

Adapted from the European Society for Vascular Surgery (ESVS) Clinical Practice Guidelines (2022), Society for Vascular Surgery/American Venous Forum/American Vein and Lymphatic Society Guidelines (2023), and Martínez-Zapata et al. (2016)(1,3,36)

5. OTC Medicines, Dietary Supplements and Cosmetics Available in Austria and Serbia

The pharmaceutical markets of Serbia and Austria offer a wide range of products intended for the prevention and treatment of CVI. Depending on the national regulatory framework, these products are available as prescription-only medicines, over-the-counter (OTC) medicines, traditional herbal medicinal products, dietary supplements, or topical cosmetic preparations.

According to current European guidelines, pharmacological treatment should be used together with compression therapy and lifestyle modifications, particularly in patients with symptomatic CVD. Pharmacological therapy is considered an adjunct to non-pharmacological measures rather than a replacement for them. (1)

Table 4 provides an overview of the principal venoactive medicines, dietary supplements and cosmetic preparations currently available in Serbia and Austria. The information was compiled using the official ALIMs (Medicines and Medical Devices Agency of Serbia) and BASG (Austrian Federal Office for Safety in Health Care) databases and supplemented, where appropriate, with information from manufacturers and community pharmacies. Products are compared according to their active substances, pharmaceutical forms, standard dosages and regulatory status.

Table 4: Comparative Overview of Representative Venoactive Medicines, Dietary Supplements and Cosmetic Preparations Available in Serbia and Austria

Active substance (ATC code)	Representative product(s)	Pharmaceutical form	Standard dosage	Austria	Serbia
Micronized purified flavonoid fraction (MPFF) (C05CA53)	Daflon®, Dioscomb®	Film-coated tablets (500 mg)	1000 mg/day	OTC/P	—
	Detralex®, Venosmin®, Descari®	Film-coated tablets (500 mg, 1000 mg); chewable tablets (1000 mg*)	1000–2000 mg/day	—	OTC
Diosmin (C05CA03)	Diosmin Genericon®, Diosmin	Film-coated tablets (500 mg, 1000 mg)	500–1000 mg/day	OTC/P	—

	STADA®				
	Phlebodia®, Flebaven®	Film-coated tablets (500 mg, 600 mg, 1000 mg)	600–1000 mg/day	—	OTC
Sulodexide (B01AB11)	Vessel®	Soft capsules	250–500 LSU/day	—	Rx
Calcium dobesilate (C05CX01)	Doxium®	Capsules (500 mg)	500–1500 mg/day	P	—
	Doxi-Hem®	Capsules (500 mg)	500–1500 mg/day	—	Rx
Hydroxyethylrutosides (C05CA04)	Venoruton®	Capsules (300 mg); effervescent tablets (500 mg, 1000 mg); powder for oral solution; topical gel	Oral: 500– 1000 mg/day; topical: twice daily	OTC/P	—
	Avaricon®	Capsules (300 mg); topical gel	Oral: 300 mg three times daily; topical: 2– 4 times daily	—	OTC
Horse chestnut extract (Aescin)	Venosin retard®, Venostasin®	Capsules; cream; gel	According to product information	OTC/P	—
	Venogel®	Topical gel	Topical application	—	Cosmetic
Red vine leaf extract	Antistax®	Film-coated tablets (360 mg); gel; spray	360 mg once daily; topical twice daily	THMP/ Cosmetic	—
Heparin sodium (C05BA03)	Lioton 1000®	Gel (1000 IU/g)	Topical 2– 4 times daily	OTC/P	OTC

	Hepathrombin®	Gel	Topical 2–4 times daily	—	OTC
Heparin sodium + dexpanthenol	Venobene®	Ointment	Topical application	OTC/P	—
Mucopolysaccharide polysulfate (C05BA01)	Hirudoid®	Cream; gel	Topical 2–3 times daily	OTC/P	—
Multi-component flavonoid / herbal preparations	Erbaven® Retard; Erbaven® Fresh	Prolonged-release tablets; topical gel	1 tablet/day; topical twice daily	—	DS/ Cosmetic
Flavonoid-based dietary supplement	Venodia Plus®	Tablets; cream-gel	1 tablet/day	—	DS/ Cosmetic

*Pharmacy-only (P); Prescription-only (Rx); Dietary supplement (DS); Traditional Herbal Medicinal Product (THMP)

5.1. Comparison of the Serbian and Austrian Pharmaceutical Markets

The comparison presented in Table 4 shows several differences between the pharmaceutical markets of Serbia and Austria. Both countries provide access to the main evidence-based venoactive drugs used in the management of CVI. However, differences can be observed in the number of available products, their regulatory classification and the range of formulations available on each market.

The Serbian market offers a broader selection of OTC medicines, dietary supplements and cosmetic preparations. In addition to established medicinal products, patients can choose from various multi-component dietary supplements and topical formulations containing flavonoids and plant extracts.

In Austria, the market is mainly focused on medicinal products and traditional herbal medicinal products available through pharmacies. Standardized preparations such as diosmin, hydroxyethylrutosides, horse chestnut extract and red vine leaf extract represent the main pharmacological options available in Austrian pharmacies. Compared with Serbia, the number of dietary supplements and cosmetic products intended for the management of chronic venous disease is smaller.

Another notable difference is the availability of topical products. While the Serbian market includes a larger number of cosmetic preparations containing plant extracts, the Austrian market offers a wider selection of standardized topical medicinal products, including heparin-containing preparations and traditional herbal medicines.

Despite these differences, the therapeutic approach in both countries is similar. Pharmacological treatment is used together with compression therapy and lifestyle modifications, while the choice of a specific product depends on product availability, regulatory status and individual patient needs.

6. Role of the Pharmacist in the Management of Patients Receiving Venoactive Therapy

6.1. Pharmaceutical Counselling

Because many venoactive medicines are available without a prescription, pharmacists are often the first healthcare professionals consulted by patients with symptoms of CVD. During these consultations, the pharmacist helps identify patients who are suitable for self-medication and those who should be referred to a physician for further evaluation.(40,41)

The patient's symptoms should be evaluated, including their duration and severity. Risk factors such as prolonged standing, obesity, pregnancy, or a family history of chronic venous disease should also be taken into account. Based on this assessment, an appropriate OTC medicine, dietary supplement, or topical preparation may be recommended.

An important part of patient counselling is explaining the differences between registered medicines, dietary supplements, and cosmetic preparations. Patients should be informed that registered medicines have demonstrated efficacy and safety through clinical studies and regulatory approval. In contrast, dietary supplements and cosmetic products are intended as supportive measures and should not replace evidence-based pharmacological treatment when this is indicated.(1)

It is important to explain that symptom improvement is gradual and that regular use is necessary to achieve the full therapeutic effect. The importance of combining pharmacological treatment with compression therapy and appropriate lifestyle modifications should also be emphasized.

6.2. Follow-up and Monitoring of Therapy

The pharmacist also plays an important role in monitoring the effectiveness and safety of venoactive therapy after treatment has been initiated. During follow-up consultations, patients should be asked whether their symptoms have improved, whether they are taking the medication as recommended, and whether they have experienced any adverse effects. (40,41)

Although venoactive drugs are generally well tolerated, mild gastrointestinal adverse effects or local skin reactions may occur. Pharmacists should encourage patients to report persistent or unexpected adverse effects and seek medical advice when appropriate. (1)

Medication review is particularly important in older patients, who often receive treatment for several chronic conditions.

Pharmacists should assess the patient's medication profile, identify potential drug interactions, and provide appropriate recommendations when necessary. (41)

Regular follow-up by the pharmacist helps patients use venoactive drugs safely and effectively and supports long-term treatment outcomes. (40,41)

6.3. Recognition of Red Flag Symptoms

Although many patients with chronic venous disease can be managed in the community pharmacy, pharmacists should be able to recognize warning signs ("red flag" symptoms) that require medical evaluation. Early identification of these "red flag" symptoms helps ensure timely diagnosis and appropriate treatment.

Patients presenting with sudden unilateral leg swelling, severe pain, redness or warmth should be referred immediately to a physician, as these symptoms may indicate deep vein thrombosis. Likewise, patients with venous leg ulcers, signs of skin infection, or rapidly worsening symptoms should be advised to seek further medical assessment.(1)

Pharmacists should also refer patients whose symptoms do not improve despite appropriate treatment or who experience recurrent symptoms that interfere with their daily activities. Timely referral is an important part of pharmaceutical care and helps ensure appropriate patient management. (40,41)

6.4. The Role of the Pharmacist in Serbia and Austria

The role of pharmacists has undergone substantial transformation throughout history. While their traditional responsibilities included the preparation, dispensing, and optimization of medicines according to medical prescriptions, contemporary pharmacists have assumed a broader role in healthcare by promoting the safe, effective, and rational use of pharmacotherapy. In line with the 21st-century priorities of improving quality of life, health outcomes, and patient safety, the scope of pharmacy practice has expanded to include active participation in healthcare delivery and public health initiatives. (42)

Pharmacists play an important role in the management of CVD in both Serbia and Austria. In both countries, they provide patient counselling, recommend appropriate non-prescription treatment, support adherence and explain the importance of lifestyle modifications.

The Serbian market offers a wider range of OTC medicines, dietary supplements and cosmetic preparations for patients with chronic venous disease. Pharmacists therefore have an important role in explaining the differences between registered medicines, dietary supplements and cosmetic products. This helps patients choose an appropriate product and use it correctly.

In Austria, the market is more focused on standardized medicinal products and pharmacy-only medicines (*Apothekenpflichtig*). Pharmacists mainly support the appropriate selection and safe use of registered medicines.

In both countries, they also help to recognize symptoms that require medical evaluation and refer patients to a physician when necessary.(1,40,41)

Despite differences in product availability and regulatory classification, pharmacists remain key healthcare professionals in ensuring the safe and effective management of CVD.

7. Conclusion

Chronic venous disease is a common and progressive condition that can significantly affect patients' quality of life if left untreated. Early recognition of symptoms and timely initiation of treatment are essential for slowing disease progression. The findings presented in this thesis highlight the importance of evidence-based management and provide a comparative overview of the therapeutic approaches and pharmaceutical markets in Serbia and Austria.

This review also confirms that venoactive drugs have an important place in the conservative management of chronic venous disease. The greatest benefit of venoactive therapy is achieved when treatment is initiated in the early stages of the disease and combined with compression therapy and appropriate lifestyle modifications. Current evidence supports their role in improving venous symptoms, reducing oedema, and enhancing patients' quality of life. Despite differences in product availability and regulatory classification, the overall therapeutic approach to chronic venous disease is similar in Serbia and Austria. Current European clinical guidelines provide the basis for treatment in both countries, while the main differences are related to the availability and regulatory status of individual products.

Pharmacists play an important role in supporting the rational use of venoactive drugs through patient counselling, monitoring of therapy, and the recognition of symptoms that require medical evaluation. They also contribute to improving adherence, promoting evidence-based treatment, and supporting patients throughout the management of chronic venous disease.

Overall, this thesis highlights the importance of the evidence-based use of venoactive drugs, supported by appropriate pharmaceutical care, in achieving effective long-term management of chronic venous disease.

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