VIARTRIL®-S

Glucosamine Sulphate
750mg Film-Coated Tablet

1. NAME OF MEDICINAL PRODUCT

Viartril-S 750 mg Film-Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains: Crystalline glucosamine sulfate 942 mg, equivalent to 750 mg glucosamine sulphate and 192 mg sodium chloride.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM AND PRESENTATION

Film-coated tablets.
Unmarked oblong white film-coated tablets without a score line.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of the symptoms of osteoarthritis, i.e., pain and function limitation

4.2 Posology and method of administration

Posology:
The recommended dosage is one Viartril-S 750 mg film-coated tablet twice daily.

Paediatric population
Glucosamine should not be used in children and adolescents below the age of 18 years, since efficacy and safety of the use have not been established.

Elderly
No specific studies have been performed in the elderly, but according to clinical experience dosage adjustment is not required when treating otherwise healthy elderly patients.

Patients with impaired renal and/or liver function
In patients with impaired renal and/or liver function, no dose recommendations can be given, since no studies have been performed.

Glucosamine is not indicated for the treatment of acute painful symptoms since pain relief may not be experienced until after some weeks of treatment and in some cases even longer.
If no relief of symptoms is experienced after 2-3 months, continued treatment with glucosamine should be reconsidered.

Method of administration:
The film-coated tablet should be taken unchewed with plenty of fluid, preferable in the morning and in the evening with the meals.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

The product must not be given to patients who are allergic to shellfish as the active ingredient is obtained from shellfish.

4.4 Special warnings and precautions for use

In asthmatic patients, the product should be used with caution as these patients could be more susceptible to develop an allergy reaction to glucosamine with a possible exacerbation of their symptoms.

This medicinal product contains sodium which should be taken into consideration by patients on a controlled sodium diet.

No special studies were performed in patients with renal or hepatic insufficiency. The toxicological and pharmacokinetic profile of the product does not indicate limitations for these patients. However, administration to patients with severe hepatic or renal insufficiency should be under medical supervision.

Caution is advised when treating patients with impaired glucose tolerance. Closer monitoring of blood sugar levels and, where relevant, insulin requirements may be necessary at the beginning of treatment and at regular intervals during treatment.

Glucosamine should not be used in children and adolescents below the age of 18 years since safety and efficacy of use have not been established.

The presence of other joint disease which would require alternative treatment should be excluded.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed. However, the physico-chemical and pharmacokinetic properties of glucosamine sulfate suggest a low potential for interactions. In addition, glucosamine sulfate was found not to inhibit or to induce any of the major human CYP450 enzymes. In fact, the compound does not compete for absorption mechanisms and, after absorption, does not bind to plasma proteins, while its metabolic fate as an endogenous substance incorporated

in proteoglycans or degraded independently of the cytochrome enzyme system, is unlikely to give rise to drug interactions.

An increased effect of coumarinic anticoagulants during concomitant treatment with glucosamine sulfate has been reported. Therefore, a closer monitoring of the coagulation parameters may be considered in these patients when initiating or ending glucosamine therapy.

The oral administration of glucosamine sulfate can enhance the gastrointestinal absorption of tetracyclines but the clinical relevance of this interaction is probably limited.

Steroidal or non-steroidal analgesic or anti-inflammatory agents can be administered together with glucosamine sulfate.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no adequate data from the use of glucosamine in pregnant women. Glucosamine should not be used during pregnancy.

Lactation
It is not known whether or not glucosamine is excreted in human milk. The use of glucosamine during lactation is not recommended as there is no data available on the safety of the newborn.

4.7 Effects on ability to drive and use machine

No studies on the effects on the ability to drive and use machines have been performed. No important effects on the CNS or motor system are known that might impair the ability to drive or use machines. However, caution is recommended if headache, somnolence, tiredness, dizziness or visual disturbances are experienced.

4.8 Undesirable effects

The reported undesirable effects have been observed in a low proportion of patients. They are usually mild and transitory, which includes:

- ***Cardiovascular***: Peripheral oedema, tachycardia were reported in a few patients following larger clinical trials investigating oral administration in osteoarthritis. Causal relationship has not been established.
- ***Central nervous system***: Drowsiness, headache, insomnia have been observed rarely during therapy (less than 1%).
- ***Gastrointestinal***: Nausea, vomiting, diarrhoea, dyspepsia or epigastric pain, constipation, heartburn and anorexia have been described rarely during oral therapy with glucosamine.
- ***Skin***: Skin reactions such as erythema and pruritus have been reported with therapeutic administration of glucosamine.

Evaluation of the undesirable effects is based on the following frequency information:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1000 to < 1/100
Rare: ≥ 1/10000 to < 1/1000
Very rare: ≤ 1/10000
Not known: Frequency cannot be estimated from the available data

System Organ Class	Common	Uncommon	Not Known
Immune system disorders			Allergy reaction (hypersensitivity)
Metabolism and nutrition disorders			Diabetes inadequate control
Psychiatric disorders			Insomnia
Nervous system disorders	Headache Somnolence		Dizziness
Eye disorders			Visual disturbance
Cardiac disorders			Cardiac arrhythmias e.g. Tachycardia
Vascular disorders		Flushing	
Respiratory, thoracic and mediastinal disorders			Asthma Exacerbation of asthma
Gastro-intestinal disorders	Nausea Abdominal pain Dyspepsia Flatulence Diarrhea Constipation		Vomiting
Hepatobiliary disorders			Jaundice
Skin and subcutaneous tissue disorders		Erythema Pruritus Rash	Angioderma Urticaria
General disorders and administration site conditions	Tiredness		Oedema Peripheral oedema
Investigations			Hepatic enzyme elevation Blood glucose increased Blood pressure increased INR fluctuation

Cases of hypercholesterolemia have been reported, but a causal link has not been established.

4.9 Overdose

No cases accidental or intentional overdose are known. Based on acute and chronic toxicity studies in animals, symptoms of toxicity are not likely to occur at doses up to 200 times the therapeutic dose.

If overdose occurs treatment should be discontinued, symptomatic and standard supportive measures should be adopted as required e.g. act to restore the hydroelectrolytic balance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other anti-inflammatory and anti-rheumatic agents, non-steroidal anti-inflammatory drugs.
ATC code: M01AX05

Mechanism of action:
Glucosamine sulfate is the sulfate salt of the endogenous amino-monosaccharide glucosamine, a normal constituent and preferred substrate for the synthesis of glycosaminoglycans and proteoglycans in cartilage matrix and synovial fluid.

Early in vitro studies have shown that glucosamine sulfate stimulates the synthesis of glycosaminoglycans and thus of articular cartilage proteoglycans. However, glucosamine sulfate has been more recently shown to inhibit the interleukin-1 β (IL-1 β) intracellular signaling pathway via blockade of the intracellular activation and nuclear translocation of nuclear factor kappa B (NF-κB) in the cartilage chondrocytes and other relevant cells.

Pharmacodynamic effects:
Early in vitro studies have demonstrated that glucosamine sulfate has anabolic and anticatabolic effects on cartilage metabolism; sulfate ions may contribute to the pharmacological effects exerted by glucosamine by controlling the rate of glycosaminoglycan and proteoglycan synthesis and inhibiting cartilage degrading enzymes.

More recent studies have postulated that glucosamine sulfate decreases IL-1 β mediated effects, thus inhibiting a cascade of events that lead to joint inflammation and cartilage damage, such as the synthesis of metalloproteases, cyclooxygenase-2 and extracellular matrix proteins that are absent in normal cartilage, the release of nitric oxide and of prostaglandin E2, the inhibition of chondrocyte proliferation and the induction of cell death. Differently from NSAIDs, glucosamine does not directly inhibit cyclooxygenase activities. Human chondrocyte cell models have shown that crystalline glucosamine sulfate inhibits IL-1-stimulated gene expression at glucosamine concentrations similar to or lower than those found in plasma and synovial fluid of knee osteoarthritis patients receiving the drug at the therapeutic dose of 1500 mg once daily. Animal models confirmed the potential of glucosamine sulfate at human equivalent doses in delaying the progression of the disease and alleviating its symptoms.

Clinical efficacy and tolerability:
The safety and efficacy of glucosamine sulfate have been confirmed in clinical trials for treatment up to three years.

Short- and medium-term clinical studies have shown that the efficacy of glucosamine sulfate on osteoarthritis symptoms is evident already after 2-3 weeks from the beginning of administration. However, differently from NSAIDS, glucosamine sulfate has shown a duration of effect which ranges from 6 months to 3 years.

Clinical studies of daily continuous crystalline glucosamine sulfate treatment up to 3 years have shown a progressive improvement on the symptoms and a delay of the joint structural changes, as determined by plain radiography.

Glucosamine sulfate has demonstrated a good tolerability over both short-term and long-term treatment courses.

5.2 Pharmacokinetic properties

Absorption

After oral administration of 14C-labelled glucosamine, the radioactivity is rapidly and almost completely (about 90%) absorbed systemically in healthy volunteers. The absolute bioavailability of glucosamine in man after administration of oral glucosamine sulfate was 44%, due to first-pass effect of the liver. After oral administration of daily repeated doses of 1500 mg of glucosamine sulfate in healthy volunteers under fasting conditions, the maximum plasma concentrations at steady-state (Cmax,ss) averaged 1602±426 ng/ml between 1.5-4 h (median: 3 h; tmax). At steady-state, the AUC of the plasma concentrations vs. time curve was 14564±4138 ng.h/ml. It is unknown if meals significantly affect the drug oral bioavailability. The pharmacokinetics of glucosamine are linear after once daily repeated administrations in the dose interval 750-1500 mg with deviation from linearity at the dose of 3000 mg due to lower bioavailability. No gender differences were found in man with regard to the absorption and to the bioavailability of glucosamine. The pharmacokinetics of glucosamine was similar between healthy volunteers and patients with osteoarthritis of the knee.

Distribution

After oral absorption, glucosamine is significantly distributed in extra-vascular compartments including synovial fluid with an apparent distribution volume 37-fold higher than the total body water in humans. Glucosamine does not bind to plasma proteins. It is therefore highly unlikely that glucosamine might produce displacement drug interaction when co-administered with other drugs that are highly bound to plasma proteins.

Metabolism

The metabolic profile of glucosamine has not been studied because being an endogenous substance; it is used as a building block for the biosynthesis of articular cartilage components. Glucosamine is mainly metabolized through the hexosamine pathway and independently of the cytochrome enzyme system.

Crystalline glucosamine sulfate does not act as an inhibitor nor as an inducer of the human CYP450 isoenzymes including CYP 3A4, 1A2, 2E1, 2C9 and 2D6 even when tested at concentrations of glucosamine 300-fold higher than the peak plasma concentrations observed in man after therapeutic doses of crystalline glucosamine sulfate. No clinically relevant metabolic inhibition and/or

induction interactions are expected between crystalline glucosamine sulfate and co-administered drugs that are substrates of the human CYP450 isoforms.

Excretion
In man, the terminal elimination half-life of glucosamine from plasma is estimated at 15 h. After oral administration of ^{14}C-labelled glucosamine to humans, the urinary excretion of radioactivity was 10±9% of the administered dose while fecal excretion was 11.3±0.1%. The mean urinary excretion of unchanged glucosamine after oral administration in man was about 1% of the administered dose suggesting that the kidney and the liver do not significantly contribute to the elimination of glucosamine and/or of its metabolites and/or its degradation products.

Special population
Patients with renal or hepatic impairment
The pharmacokinetics of glucosamine were not investigated in patients with renal or hepatic insufficiency. Studies in renal impaired patient were considered irrelevant due to the limited contribution of the kidney to the elimination of glucosamine. Similarly, studies in subjects with hepatic impairment were not conducted given glucosamine metabolic fate as an endogenous substance. Therefore, for what described above and in light of the good safety and tolerability profile of glucosamine, no dose adjustment is considered necessary in subjects with renal or hepatic insufficiency.

Children and adolescents
The pharmacokinetics of glucosamine was not investigated in children and adolescents.

Elderly patients
No specific pharmacokinetic studies were performed in elderly however in the clinical efficacy and safety studies mainly elderly patients were included. Dose adjustment is not required.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Povidone K 25, Croscarmellose sodium, Macrogol 6000, Magnesium stearate, Talc, Methacrylic acid - methyl methacrylate copolymer (1:1), Titanium dioxide, Ammonium methacrylate copolymer (type A), Triacetin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date shall be applicable to the properly stored product in its intact packaging. Do not use the product after expiry date indicated on the label.

6.4 Special precautions for storage

Do not store above 30°C.
Keep out of reach of children / Jauhi daripada kanak-kanak.

6.5 Nature and contents of container

Immediate packaging: Polyethylene bottle
Secondary packaging: Carton containing a bottle filled with 60 film-coated tablets.

6.6 Special precautions for disposal

Not applicable.

7. MANUFACTURER

Madaus GmbH
Lütticher Straße 5
53842 Troisdorf
Germany

8. PRODUCT REGISTRATION HOLDER

Mylan Healthcare Sdn Bhd
15-03 & 15-04, Level 15, Imazium,
No. 8, Jalan SS 21/37, Damansara Uptown,
47400 Petaling Jaya, Selangor, Malaysia

9. DATE OF REVISION

June 2024