Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Viartril 1500 mg Powder for Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 1884 mg glucosamine sulfate sodium chloride, equivalent to 1500 mg glucosamine sulfate and 384 mg sodium chloride.

Excipients: Each sachet contains 2.5 mg aspartame (E951), 2028.5 mg sorbitol (E420) and 151 mg sodium.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for oral solution
A white, crystalline, odourless powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of symptoms in mild to moderate osteoarthritis of the knee, as diagnosed by a doctor.

4.2 Posology and method of administration

The contents of one sachet (dissolved in a glass of water) should be taken once daily, preferably at meals.
Pivotal proof of efficacy has been demonstrated for periods of up to three months, with a residual effect evident for two months after drug withdrawal. The safety and efficacy of the product were also confirmed in pivotal clinical trials for treatment up to three years. Continuous treatment beyond 3 years cannot be recommended as the safety has not been established beyond this period.

Glucosamine is not indicated for the treatment of acute painful symptoms. Relief of symptoms (especially 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 re-evaluated by the patient's healthcare practitioner.

Patients should seek medical advice if their symptoms deteriorate after commencing treatment with glucosamine.

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

Patient 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 (see also section 4.4).

Children and adolescents:
Glucosamine should not be used in children and adolescents below the age of 18 years (see section 4.4).

4.3 Contraindications

Hypersensitivity to glucosamine or to any of the excipients listed in section 6.1. The powder for oral solution contains aspartame and is therefore contraindicated in patients with phenylketonuria.

The powder for oral solution contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this pharmaceutical form.

The product should 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

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

Exacerbation of asthma symptoms after initiation of glucosamine have been described. Therefore, asthmatic patients starting on glucosamine should be aware of potential worsening of symptoms.

Caution is advised in treatment of patients with impaired glucose tolerance. Closer monitoring of blood sugar levels and where relevant insulin requirements may be necessary in diabetics at the beginning of treatment and periodically during treatment.

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.

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

If unusual signs or symptoms appear, or if any changes in the course of usual symptoms occur, the patient is recommended to consult the physician immediately.

This medicinal product contains:

- 2028.5 mg sorbitol per sachet. Patients with hereditary fructose intolerance (HFI) should not take this medicine.
- 2.5 mg aspartame in per sachet. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.
- 151 mg sodium per sachet, equivalent to 7.6 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

There are limited data on possible drug interactions with glucosamine, but increments in the INR parameter have been reported with oral vitamin K antagonists. Patients treated with oral vitamin K antagonists should therefore be closely monitored at the time of initiation or termination of glucosamine therapy.

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 one study Glucosamine was found not to be an inhibitor of the activities of the following human cytochrome P450 enzymes: CYP1A2, CYP2E1, CYP2C19, CYP2C9, CYP2D6, CYP3A4, as tested by metabolite formation from selected substrates for each of the CYP enzymes tested. The compound does not compete for absorption mechanisms and, after absorption, does not bind to plasma protein, 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.

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-steriodal 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. From animal studies only insufficient data are available. Glucosamine should not be used during pregnancy.

Breast Feeding
There is no data available on the excretion of glucosamine in human milk. The use of glucosamine during breastfeeding is therefore not recommended as there is no data on the safety of the newborn.

4.7 Effects on ability to drive and use machines

No studies of 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 imparie the ability to drive or use machines. However, if headache, somnolence, tiredness, dizziness or visual disturbances are experienced, driving a car or operating machinery is not recommended (see section 4.8).

4.8 Undesirable effects

Within the system organ classes, adverse reactions are listed under the frequency (number of patients expected to experience the reaction), using the following categories:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

The following undesirable effects were observed whereas the frequency of undesirable effects is not known:

The most common adverse reactions associated with oral administration are nausea, abdominal pain, dyspepsia, flatulence, constipation and diarrhoea. The reported adverse reactions are usually mild and transitory.

In the following table, adverse reactions have been grouped on the basis of "Internationally agreed Order of Importance" System Organ Class (SOC) MedDRA Classification. In each SOC, undesirable effects were classified according to their occurrence frequency. In each frequency class the undesirable effects are reported according to a decreasing order of severity.

System Organ Class	Very common ≥1/10	Common from ≥1/100 to ≤1/10	Uncommon from ≥1/1,000 to ≤1/100	Rare from ≥1/10,000 to ≤1/1,000	Very rare ≤1/10,000	Unknown*
Immune system disorders						Allergic reaction**
Metabolism and nutrition disorders						Diabetes inadequate control
Psychiatric disorders						Insomia
Nervous system disorders		Headache Somnolence				Dizziness
Eye disorders						Visual disturbances
Cardiac disorders						Cardiac arrhythmias e.g. tachycardia
Vascular			Flushing			
Respiratory, thoracic and mediastinal disorders						Asthma/aggravated asthma
Gastrointestinal disorders		Diarrhoea Constipation Nausea Flatulence				vomiting

		Abdominal pain Dyspepsia				
Skin and subcutaneous tissue disorders			Erythema Pruritus Rash			angiodema, urticaria
Hepatobiliary disorders						Hepatic enzyme increased and jaundice***
General disorders and administration site conditions		Tiredness				Oedema/peripheral oedema
Investigations						Hepatic enzyme elevation, blood glucose increased, blood pressure increased, international normalized ratio fluctuation

* which frequency cannot be estimated by the available data
**Predisposed patients might develop severe allergic reactions to glucosamine
***Cases of hepatic enzymes increase and jaundice have been reported, but causality with Viartril has not been established.

Cases of hypercholesterolaemia have been reported, but a causal link has not been demonstrated

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

No cases of accidental or intentional overdose are known. The animal acute and chronic toxicological studies indicate that toxic effects and symptoms are unlikely 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 hydroelectrolyte balace.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other anti-inflammatory and anti-rheumatic agents, non-steroidal anti-inflammatory drugs.

(Product for the musculoskeletal system - 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 syntheses of glycosaminoglycans and proteoglycans in cartilage matrix amd synovial fluid.

Early *in vitro* studies have shown that glucosamine sulfate stimulates the synthesis of glycosaminoglycans and this 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 in the cartilage chondrocytes and other relevant cells.

Pharmacodynamic effects:
Early in vitro studies have demonstrated that glucosamine sulfate has anabolic and anti-catabolic 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 1500mg once daily. Animal models confirmed the potential of glucosamine sulfate at human equivalent does in delaying the progression of the disease and alleviating its symptoms.

Clinical efficacy and tolerability:
The safety and efficacy of glucosamine sulfate has been confirmed in clinical trials for treatment of 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 health 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 14C-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 suggestion 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.

Older people

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

5.3 Preclinical safety data

Nonclinical data revealed no special hazard for humans based on conventional studies of single and repeated dose toxicity and genotoxicity.

In non-clinical studies in rats, adverse effects on fertility, embryo/foetal development and postnatal development were not observed. In rabbits, cases of maternotoxicity (deaths due to gastric bleeding) and foetoxicity (increased resorption rate) were observed, but only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Results from some in vitro and in vivo studies in animals, have shown that i.v. infusion of glucosamine in suprapharmacological concentrations reduces insulin secretion, probably via inhibition of glucokinase in the beta cells, and induces insulin resistance in peripheral tissues. The relevance in humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)
Macrogol 4000
Citric acid, anhydrous (E330)
Sorbitol (E420)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The single dose sachet consists of three layers of material made of paper, aluminium and polyethylene.

Cardboard box containing 4, 20 or 30 sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Cooper Consumer Health B.V.
Verrijn Stuartweg 60
Diemen
Noord-Holland
1112 AX
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA25506/002/001

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