swissmedic

Date: 27 February 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Condrosulf Plus

International non-proprietary name: chondroitin sulfate sodium, glucosamine hydrochloride

Pharmaceutical form: hard capsule

Dosage strength(s): 200 mg chondroitin sulfate sodium
250 mg glucosamine hydrochloride

Route(s) of administration: oral

Marketing authorisation holder: IBSA Institut Biochimique SA

Marketing authorisation no.: 68626

Decision and decision date: approved on 11 January 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, definitions, abbreviations 3

2 Background information on the procedure 4

2.1 Applicant's request(s) 4

2.2 Indication and dosage 4

2.2.1 Requested indication 4

2.2.2 Approved indication 4

2.2.3 Requested dosage 4

2.2.4 Approved dosage 4

2.3 Regulatory history (milestones) 4

3 Quality aspects 5

3.1 Drug substance 5

3.2 Drug product 6

3.3 Quality conclusions 6

4 Non-clinical aspects 7

5 Clinical and clinical pharmacology aspects 7

6 Risk management plan summary 7

7 Appendix 8

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

1 Terms, definitions, abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for glucosamine hydrochloride in the above-mentioned medicinal product.

Authorisation in accordance with Article 14 para. 1 a^{bis} TPA
The applicant requested a simplified authorisation procedure in accordance with Article 14 para. 1 a^{bis} TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Condrosulf Plus is indicated for the symptomatic treatment of knee osteoarthritis in patients with moderate to severe pain.

2.2.2 Approved indication

Symptomatic treatment of knee osteoarthritis in adult patients with moderate to severe pain.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The dosage is two hard capsules three times a day (= 1200 mg chondroitin sulfate/1500 mg glucosamine) for at least 6 months. Safety and efficacy have not been demonstrated in children and adolescents.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	2 August 2021
Formal control completed	30 September 2021
List of Questions (LoQ)	26 January 2022
Response to LoQ	13 April 2022
Preliminary decision	22 July 2022
Response to preliminary decision	10 October 2022
Final decision	11 January 2023
Decision	approval

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

3 Quality aspects

Condrosulf plus is a combination preparation containing the active substances chondroitin sulfate sodium (known active substance) and glucosamine hydrochloride (new active substance). The dosage strength is 200 mg chondroitin sulfate sodium and 250 mg glucosamine hydrochloride in hard capsules.

3.1 Drug substance

Drug substance glucosamine hydrochloride

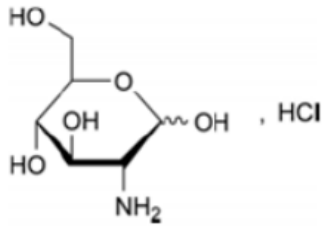
INN and compendial name: Glucosamine hydrochloride

Chemical name: 2-Amino-2-deoxy-D-glucopyranose hydrochloride

Molecular formula: $C_6H_{14}ClNO_3$

Molecular mass: 215.6 g/mol

Molecular structure:



Physico-chemical properties:

Glucosamine hydrochloride is a white or almost white, crystalline powder, which is freely soluble in water. The configuration is a D-amino sugar, during the isolation process there is no potential for epimerisation. Glucosamine hydrochloride is found in nature as a single crystal structure.

Synthesis:

Glucosamine hydrochloride is a semi-synthetic drug substance, obtained by acidic hydrolysis of chitin, which is isolated from crustacean shells. The purification process comprises filtration, washing and precipitation steps.

Specification

Glucosamine hydrochloride complies with Ph. Eur. 2446.

Stability:

Based on the stability data submitted, the proposed storage conditions and re-test period of the drug substance in its commercial container are considered satisfactory.

Drug substance – chondroitin sulfate sodium

INN and compendial name: Chondroitin sulfate sodium

Chemical name: Natural copolymer based mainly on the 2 disaccharides:

[4)-(β-D-gluco-pyranosyluronic acid)-(1→3)-[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl 4-sulfate]-(1→]

and

[4)-(β-D-glucopyranosyluronic acid)-(1→3)-[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl 6-sulfate]-(1→], sodium salt

Molecular formula: $H_2O(C_{14}H_{19}NNa_2O_{14}S)_x$

Molecular mass: 503.3

Since chondroitin sulfate sodium is obtained from bovine tissue, the material meets the criteria of Ph. Eur. 1483. The manufacturing process, including starting materials, is certified by EDQM to comply with Ph. Eur. 5.2.8 and to be sufficiently controlled by the Ph. Eur. monograph Chondroitin sulfate sodium, terrestrial (2064).

Stability:

Based on the stability data submitted, the proposed storage conditions and re-test period of the drug substance in its commercial container are considered satisfactory.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

3.2 Drug product

Description and composition:
Condrosulf Plus consists of an immediate-release gelatin hard capsule of turquoise colour containing a fixed dose combination of 200 mg chondroitin sulfate sodium and 250 mg glucosamine in powder form. There is only one excipient – magnesium stearate – in the capsule fill. The hard capsule contains gelatin, indigo carmine (E132) and titanium dioxide (E171) as an excipient.

Manufacture:
The manufacturing process is a conventional standard process that comprises several sifting and blending steps and an encapsulation step. Process parameters and in-process controls are defined in order to ensure consistent capsule quality. Satisfactory manufacturing process validation has been performed on three consecutive production-scale batches.

Specification:
Adequate tests and acceptance criteria for release and shelf-life are in place for the control of the finished product, covering parameters such as identity, appearance, assay, related substances, loss on drying, dissolution, uniformity of dosage units and microbial quality. All routine tests either comply with the requirements of Ph. Eur. or have been described and validated.

Container closure system:
Condrosulf Plus is packaged in a PVC/PVDC/aluminium blister.

Stability:
Appropriate stability data were submitted for three commercial-scale stability batches. Based on these data, the shelf-life was defined as 48 months. The storage recommendation is “Do not store above 30°C”.

3.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

4 Non-clinical aspects

In accordance with Art. 14 para. 1 a^{bis} TPA, Swissmedic has only reviewed the nonclinical overview for the authorisation of Condrosulf Plus. The approval of Condrosulf Plus is based on the medicinal product Droglican 200 mg/250 mg cápsulas duras, which contains the same active substances and has been authorised in Spain for more than 10 years.

5 Clinical and clinical pharmacology aspects

In accordance with Art. 14 para. 1 a^{bis} TPA, Swissmedic has conducted only a summary review of efficacy and safety for the authorisation of Condrosulf Plus. The approval of Condrosulf Plus is based on the medicinal product Droglican 200 mg/250 mg cápsulas duras, which contains the same active substances and has been authorised in Spain for more than 10 years.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Condrosulf Plus was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Condrosulf Plus

The efficacy and safety of Condrosulf Plus have only been summarily assessed by Swissmedic. The authorisation of Condrosulf Plus is based on Droglican as of March 2018, which contains the same active substances and is authorised in Spain.

Composition

Active substances

Chondroitin sulphate sodium (bovine), Glucosamine hydrochloride (shellfish).

Excipients

Contains per capsule: 18 mg (0.8 mmol) sodium, magnesium stearate, gelatine, titanium dioxide (E171), indigo carmine (E132).

Dosage form and active substance quantity per unit

Capsules of 200 mg chondroitin sulphate sodium and 250 mg glucosamine hydrochloride.

Indications/applications

Symptomatic treatment of knee osteoarthritis in adult patients with moderate to severe pain.

Posologie/Application

The recommended dose is 2 capsules taken 3 times a day (1'200 mg/day chondroitin sulphate and 1'500 mg/day glucosamine hydrochloride). The success of the treatment should be checked after about 12 weeks of treatment and at regular intervals thereafter.

Kidney and/or renal failure:

In patients with impaired renal and/or liver function no dose recommendations can be given,

since no studies have been performed.

Children and young people

The safety and efficacy in children and adolescents has not been shown.

Type of application

The capsules can be taken before, during or after meals. Patients with a clinical history of gastric intolerance to medicines in general are recommended to take it after meals.

The capsules should be swallowed whole, without chewing, and with a sufficient amount of liquid.

Contraindications

Hypersensitivity to the active substances or to one of the excipients according to the composition.
Condrosulf Plus must not be given to patients who are allergic to shellfish, as one of the active ingredients (glucosamine) is derived from shellfish.

Warnings and precautions

Results from non-clinical studies have shown that glucosamine reduces insulin secretion and can increase insulin resistance. The clinical relevance of this effect is uncertain. Nevertheless, in patients with impaired glucose tolerance, monitoring of the blood glucose levels and, where relevant, of insulin requirements is recommended, before start of treatment and periodically during treatment.

Cardiac and/or renal failure:
In very rare cases (< 1/10,000), in such patients treated with chondroitin sulfate, some cases of oedema and/or water retention have been reported. This phenomenon may be attributed to the osmotic effect of chondroitin sulfate. The daily dose of 6 capsules of Condrosulf Plus contains 108 mg of sodium (the main component of table salt). This corresponds to 5.4 % of the maximum recommended daily dietary sodium intake for an adult.

Interactions

No interaction studies between glucosamine and chondroitin sulphate have been performed.
In rats and at doses much higher than the recommended ones (50 mg/kg/day, equivalent to 4,000 mg/day in humans) a mild blood-thinning effect has been observed for chondroitin sulfate. This effect will have to be considered when used in conjunction with blood thinning drugs (acetylsalicylic acid, dipyridamole, clopidogrel, ditazole, trifusal and ticlopidine). Nevertheless, no blood-thinning effects have been detected from either clinical research or pharmacovigilance experience within the recommended dose of chondroitin sulfate.
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 discontinuation of glucosamine therapy.
Glucosamine may increase the absorption and serum concentration of tetracyclines and reduce the absorption of penicillin and chloramphenicol.

Pregnancy, lactation

Pregnancy

There are no data available on the use of chondroitin sulphate and glucosamine in pregnant women. Animal studies are not sufficient to determine the effects on pregnancy and/or embryonic, foetal or postnatal development. Therefore, this medicinal product is not recommended to be used during pregnancy.

Breastfeeding

It is unknown whether chondroitin sulphate or glucosamine are excreted into human breast milk. Therefore, and due to the lack of safety information on the newborn, the use of this medicinal product during breastfeeding is not recommended.

Effect on the ability to drive and operate machinery

No studies on the effects on the ability to drive and use machines have been performed.
If dizziness or drowsiness is experienced, driving and operating machinery is not recommended.

Adverse effects

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); unknown (cannot be estimated from available data).
In the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), a multicenter, doubleblind, placebo and active-controlled study, 317 patients were treated with the combination of chondroitin sulfate and glucosamine hydrochloride, most of the adverse reactions experienced were mild and transient in nature.
The adverse events occurring in at least two patients in this study, considered at least possibly related to the combination of chondroitin sulphate and glucosamine hydrochloride, are listed below by body system organ class. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. *Diseases of the nervous system*
Common: headache.
Rare: dysgeusia.
Gastrointestinal disorders
Common: diarrhoea, nausea, dyspepsia, flatulence.
Rare: gastro-oesophageal reflux disease, abdominal pain upper, constipation, abdominal discomfort, abdominal distension.
Investigations
Rare hepatic enzyme increase, urine analysis abnormal.
Infections and infestations
Rare: upper respiratory tract infection, urinary tract infection.

General disorders and administration site conditions
Rare: fatigue.
Musculoskeletal and connective tissue disorders
Rare: muscle cramps, pain in the extremities.

The adverse events included in the summary of product characteristics of **chondroitin sulfate** are listed below, classified by body system organ class

Gastrointestinal disorders
Common: digestive disorders, gastrointestinal disorder.
Uncommon: nausea, constipation, but these do not usually require interruption of treatment.

Diseases of the skin and subcutaneous tissue
Uncommon: skin rash.

General disorders and administration site conditions

Rare: oedema and/or water retention have been observed in rare cases in patients with renal and/or cardiac insufficiency. This phenomenon could be due to an osmotic activity of chondroitin sulphate. However, the sodium content is very low, see "Composition".
Nervous system disorders
Common: headache.
Uncommon: dizziness.

The adverse events included in the summary of product characteristics of **glucosamine hydrochloride** are listed below, classified by body system organ class.

Nervous system disease
Common: headache.
Unknown: dizziness.
Gastrointestinal disorders
Common: nausea, abdominal pain, dyspepsia, diarrhoea, constipation.
Unknown: vomiting.

Skin and subcutaneous tissue disorders
Uncommon: rash, pruritus, flushing.
Unknown: angioedema, urticaria.

General diseases and administration site conditions
Unknown: oedema, peripheral oedema, fatigue.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the risk-benefit balance of the medicinal product. Healthcare professionals are asked to report any suspicion of a new or serious adverse reaction via the online portal ElViS (Electronic Vigilance System). Information on this can be found at www.swissmedic.ch.

Overdose

Signs and symptoms caused by accidental or intentional overdose with glucosamine may include headache, vertigo, disorientation, arthralgia, nausea, vomiting and diarrhoea.
In clinical trials, one in five young healthy volunteers experienced headaches after infusion of up to 30 g of glucosamine. One case of overdose was reported in a 12-year-old girl who took 28 g of glucosamine hydrochloride orally. She developed arthralgia, vomiting and disorientation. The patient fully recovered.
One case of overdose was recorded (dose: 80 tablets of 800 mg), but it had no clinical consequences for the patient (in particular, no occurrence of vomiting or nausea, no electrolyte imbalance).
In case of overdose, treatment should be discontinued and standard supportive measures should be adopted as required.
Based on the results of studies on acute and chronic toxicity, no toxic symptoms are expected even at high doses.

Properties/effects

ATC code

M01CX

Mechanism of action

Condrosulf Plus
comprises chondroitin sulfate, a polysaccharide of the glycosaminoglycan group, and glucosamine (as glucosamine hydrochloride), a natural amino monosaccharide..

Pharmacodynamics

Chondroitin sulphate is a major component of cartilage and binds with endogenous proteins to form proteoglycans, providing cartilage with its mechanical and elastic properties. . The therapeutic effect of chondroitin sulphate in patients with osteoarthritis is due to a variety of factors: anti-inflammatory [mediated by inhibition of interleukin-1β (IL-1β), metalloprotease-3 (MMP-3) and prostaglandin E2 (PGE2)]; stimulation of proteoglycan and hyaluronic acid synthesis; and inhibition of cartilage proteolytic enzymes (including collagenase, elastase, proteoglycanase, phospholipase A2, N-

acetylglucosaminidase, etc.); inhibition of the nuclear translocation of nuclear factor κB (NF-κB)involved in some chronic inflammatory processes.

Glucosamine is an endogenous substance, a constituent of the polysaccharide chain from the cartilaginous matrix and of glycosaminoglycans from the synovial fluid. In vitro and in vivo studies have evidenced that glucosamine stimulatesphysiological synthesis of glycosaminoglycans and proteoglycans by chondrocytes and the synthesis of hyaluronic acid by synoviocytes. Subsequent studies have shown that glucosamine may inhibit the synthesis of superoxide radicals and lysosomal enzyme activity, as well as cartilage-destroying enzymes, such as collagenase and phospholypase A2.
In vitro studies have shown that chondroitin sulphate and glucosamine promote the development of new cartilage by stimulating the synthesis of both collagen and proteoglycans. This effect is synergistic when both drugs are administered in combination.

Clinical efficacy

The effect of combined chondroitin sulphate and glucosamine on osteoarthritis has been evaluated in several clinical trials. The results of two of these studies are described below.

A multicentre, randomised, double-blind clinical trial involving 1583 patients with knee osteoarthritis investigated the efficacy of five treatments (500 mg glucosamine t.i.d., 400 mg chondroitin sulphate t.i.d., 200 mg celecoxib u.i.d., 500 mg glucosamine + 400 mg chondroitin sulphate t.i.d. and placebo) on pain reduction after 6 months of treatment. Results showed that glucosamine (64.0%), chondroitin sulphate (65.4%) or the combination of both treatments (66.6%) did not significantly reduce pain as compared with placebo (60%) in overall study population. The lack of statistical significance might be explained because most patients had mild pain at baseline (making it difficult to discern any improvement in pain)
and because of the high response rate of placebo (60 %) against the expected rate (35 %). Nevertheless, in the
intention-to-treat analysis from the group of patients with moderate to severe pain, the combined treatment with chondroitin sulphate and glucosamine decreased pain significantly compared to placebo (79.2 % vs. 54.3 %) in patients with knee ostheoarthritis.

A multicentre, randomised, double-blind clinical trial investigated the effect of Condrosulf Plus versus celecoxib in 606 patients with Kellgren and Lawrence grade 2-3 knee osteoarthritis and moderate to severe pain (WOMAC pain score >301). In this non-inferiority trial ($\Delta = 8$; $\sigma = 26$), the primary efficacy outcome was the mean decrease in WOMAC pain from baseline to 6 months. Secondary outcomes included WOMAC function and stiffness, visual analogue scale for pain, presence of joint

swelling/effusion, rescue medication use, Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT-OARSI) criteria and the EuroQol-5D. At 6 months, patients treated with Condrosulf Plus experienced a 50.1% (185.8 (7.4) WPS) reduction in WOMAC pain compared with 50.2% (184.7 (7.6) WPS) in the celecoxib group; the mean difference between the two treatments being 1.1 on the WOMAC pain subscale, well within the previously established non-inferiority threshold. Both groups elicited a reduction >50% in the presence of joint swelling, a similar reduction was observed for effusion. At 6 months, 79.7% of patients in the combination group and 79.2% in the celecoxib group fulfilledOMERACT-OARSI criteria. No differences were observed between treatments for the other secondary outcomes.

Pharmacokinetics

No pharmacokinetic studies have been performed with the combination.
Two glucosamine salts, hydrochloride and sulphate, have been used therapeutically and are considered prodrugs: both salts dissolve completely in the stomach where they are converted to the free glucosamine base and are readily available for absorption in the small intestine.

Absorption

Chondroitin sulphate:
Several studies demonstrate that the bioavailability of chondroitin sulfate ranges from 15 to 24% of the orally administered dose.. Of the absorbed portion of chondroitin sulphate, 10 % is in the form of chondroitin sulphate and 90 % is in the form of depolymerised derivatives of lower molecular weight, consistent with the hepatic first-pass effect. After oral administration, the maximum concentration of chondroitin sulphate in the blood is reached in about 4 hours.
Glucosamine: after oral administration, about 90 % of the glucosamine sulphate administered is absorbed in the gastrointestinal tract.

Distribution

Chondroitin sulphate: in blood, 85 % of chondroitin sulphate and its depolymerised derivatives are bound to several plasma proteins. The volume of distribution of chondroitin sulphate is relatively low (approx. 0.3 l/kg). In humans, chondroitin sulphate shows an affinity for articular tissue. In rats, in addition to joint tissue, chondroitin sulfate shows an affinity for the small intestine wall, the liver, the brain and the kidneys..
Glucosamine: no information is available on other pharmacokinetic parameters in humans, but these have been widely studied in rats and dogs using uniformly labelled^{14} C-glucosamine.
Free^{14} C-glucosamine disappears rapidly from plasma and concomitantly the radioactivity is incorporated in plasma globulins, the liver and kidneys and also in joint tissue, where concentrations are higher than in the blood.

Metabolism

Chondroitin sulphate: at least 90 % of the administered dose of chondroitin sulphate is firstlymetabolised by lysosomal sulphatases and depolymerised lately by hyaluronidases, βglucuronidases and β-N-acetylhexosaminidases. Liver, kidneys and other organs intervene in the depolymerisation process of chondroitin sulphate. No metabolic interactions with other medicinal products have been described. Chondroitin sulphate is not metabolised by cytochrome P450 enzymes

Elimination

Chondroitin sulphate: the systemic clearance of chondroitin sulphate is 30.5 ml/min or 0.43 ml/min/kg. The half-life is between 5 and 15 hours, depending on the experimental protocol. Chondroitin sulphate and its depolymerised derivatives are mainly eliminated through the kidney.
Glucosamine: about 5 % of the glucosamine is excreted in the urine in the subsequent 48 hours after oral administration. Most of the glucosamine administered orally is metabolised in the tissues and eliminated by breathas CO_2.

Linearity/Non-linearity

Chondroitin sulphate: Chondroitin sulphate shows first order kinetics for single doses of up to 3,000 mg. Multiple doses of 800 mg in patients with osteoarthritis do not alter the kinetics of chondroitin sulphate.
Glucosamine: repeated daily administration of labelled^{14} C-glucosamine sulphate shows that the active substance reaches a steady level in the blood on the third day of administration and does not accumulate after that time.
The pharmacokinetics of^{14} C-glucosamine sulphate were studied in healthy male volunteers who
were administered a single dose by the intravenous (IV), intramuscular (IM) or oral route. After oral administration, free glucosamine was not detectable in plasma. The radioactivity incorporated into plasma proteins followed pharmacokinetic patterns similar to those obtained after intravenous and intramuscular administration, but itsconcentrations in plasma were lower than those obtained after parenteral administration, probably due to a first-pass effect in the liver.

Kinetics of special patient groups

Not specified

Preclinical data

Data from non-clinical studies conducted with chondroitin sulphate and glucosamine do not indicate any special hazard for humans according to the following available studies:

- for chondroitin sulphate, according to the conventional studies on safety pharmacology, repeated-dose toxicity, mutagenicity, genotoxicity and reproductive toxicity,
- for glucosamine, according to the conventional studies on safety pharmacology, repeated-dose toxicity and genotoxicity.

Results from *in-vitro* and *in-vivo* animal studies have demonstrated that glucosamine decreases insulin secretion and increases insulin resistance, probably by inhibiting beta cell glucokinase. The clinical relevance of this effect is unknown.

Other notes

Durability

The medicinal product may only be used until the date stated on the pack as "EXP".

Special storage instructions

Do not store above 30 ºC. Store in the original packaging and out of reach of children.

Approval number

68626 (Swissmedic)

Packs

Condrosulf Plus: 90 capsules [B]

Authorisation holder

IBSA Institut Biochimique SA, Lugano

Status of the information

Foreign comparator medicinal product: March 2018
With safety-related supplements from Swissmedic: July 2022