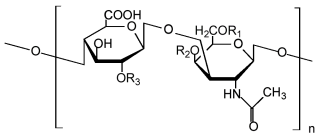
Prescriber/Physician Resource
INFORMATION NOT INTENDED FOR CONSUMERS



Chemical structure of one unit in a chondroitin sulfate chain. Chondroitin-4-sulfate: R1 = H; R2 = SO3H; R3 = H. Chondroitin-6-sulfate: R1 = SO3H; R2, R3 = H.

Generic Name:
Chondroitin Sulfate
(Pharmaceutical/prescription grade, greater than 95%)

Brand Name:
Osteosyn® by Synutra Pure: **Chondroitin 1000** and **Chondroitin 1000+** (both available in low sodium form)

Dosage Form and Strength:
Osteosyn® **Chondroitin 1000**: capsules of 500mgs each, and dosage is 2 capsules per day at 1000mgs
Osteosyn® **Chondroitin 1000+**: capsules of 250mgs each with equal amount of glucosamine hydrochloride, and dosage is 4 capsules per day at 1000mgs of chondroitin sulfate delivered

FDA Indications:
Dietary supplement for healthy join support

EMA (European Medical Agency) Indications:
Anti-osteoarthritic drug*

ESCEO (the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis) Consensus Statement:
Symptomatic slow-acting drug for osteoarthritis (SYSADOA) in background maintenance therapy*

Intended Use and Target Population: including FDA Approved Uses and Off-Label Uses:
FDA recognizes chondroitin sulfate as a dietary supplement used to provide structure and function support to healthy joint, without making qualified health claim. In European countries and South America, chondtoitin sulfate is considered a symptomatic slow-acting drug for osteoarthritis (SYSADOA). The target population includes early-to-late-stage OA patients before surgical interventions are necessary. In ongoing practice, Osteosyn Chondroitin capsules have been used with discretion as an off-label, non-invasive treatment of OA for patients not needing surgery.*

Alternative to Current Therapeutic Options:
Celecoxib, ibuprofen, naproxen, meloxicam, acetaminophen, and other name brand or generic non-steroidal anti-inflammatory drugs or NSAIDs. According to the FDA all prescription NSAIDs, like Celebrex, ibuprofen, naproxen, acetaminophen, and meloxicam, have the same cardiovascular warning. They may all increase the chance of heart attack or stroke that can lead to death. This chance increases if you have heart disease or risk factors for it, such as high blood pressure or when NSAIDs are taken for long periods. Celebrex should not be used right before or after certain heart surgeries. Serious skin reactions, or stomach and intestine problems such as bleeding and ulcers, can occur without warning and may cause death. Patients taking aspirin and the elderly are at increased risk for stomach bleeding and ulcers. Acetaminophen accounts for more than 100,000 calls to poison centers, roughly 60,000 emergency-room visits and hundreds of deaths each year in the United States. In England, it is the leading cause of liver failure requiring transplants. In 2009, the FDA issued guidelines for adding overdose guidelines to packages and in 2011, the agency confirmed the link between the drug and liver damage. No such warnings or adverse events have been reported in any country where Chondroitin is being sold as a drug such as Europe and South America.*

As stated and supported by clinical studies, chondroitin sulfate in pharmaceutical grade purity and adequate dosage (NLT 800mgs) has been proven to be safe and efficacious for treatment of symptomatic OA. In current orthopedic practices, OA treatment options remain limited with NSAIDS for pain management and invasive surgical procedures, including total joint replacement. OA patients of various stages of ailing conditions that may last for years have little options other than NSAIDs with known adverse reactions before surgery. Osteosyn® Chondroitin preparations fill the void of safe and cost-effective treatment options between pain management with NSAIDs and surgeries. Osteosyn® Chondroitin capsules provide a needed and long-term relief to patients suffering from degenerative osteoarthritis in an easy, oral form of administration.*

Common Adverse Events (Listed in order of decreasing seriousness within each frequency interval):

- Gastrointestinal disorders
  - Rare: Nausea, gastrointestinal alterations.
- General disorders and administration site conditions
  - Very rare: Edema, water retention.
- Immune system disorders
  - Very rare: Allergic reaction.

* THESE STATEMENTS HAVE NOT BEEN EVALUATED BY THE FOOD AND DRUG ADMINISTRATION. THESE PRODUCTS ARE NOT INTENDED TO DIAGNOSE, TREAT, CURE, OR PREVENT ANY DISEASE.

Death and Other Serious Adverse Events:
None has been reported.

Precautions/Contra-indications:
Hypersensitivity to the active ingredient chondroitin sulfate or to any of the excipients; When formulated with glucosamine hydrochloride, cautions include hypersensitivity to glucosamine and shellfish products; Label note: if pregnant, lactating or on prescribed medication, consult your physician before use.

Drug Interactions:
None has been reported.

Place in Therapy:
With consideration of preponderant clinical evidence on safety and efficacy of chondroitin sulfate an alternative to NSAIDs in pain management regimes of OA therapy, Osteosyn® Chondroitin capsules have been introduced for use by OA patients in orthopedic practices and various other settings. Patients have responded positively with expected improvement in pain and discomfort, range of motion, increased level of activities, and with no adverse reactions or events reported to date.*

Inclusion Criteria:
Patients seeking relief from or treatment for symptoms of degenerative osteoarthritis without needing surgical intervention.*

Dosing and Administration:
Oral administration: can be taken before, during or after a meal. Patients with a history of gastric intolerance to medicinal products in general are recommended to take after a meal. No cases of overdosing have been reported. Based on the acute and chronic toxicity results obtained, toxic symptoms are not expected, even after an elevated dose.

Monitoring Parameters:
Improvement in joint pain* and discomfort levels; changes in range of motion; changes in activity levels.

Discontinuation Criteria:
Lack of appropriate outcomes after using for 6 months, or adverse events.

Literature Review and Summary of Findings*:

- Arthritis affects one quarter of US Veterans according to a publication by the CDC.
- Prescription grade chondroitin (≤ 95% purity) that meets all the EP and BP criteria for quality has been found in numerous clinical trials to be an effective treatment for osteoarthritis and is considered a symptomatic slow-acting drug for this disease (SYSADOA) in Europe and some other countries.
- According to Dr Pelletier and his team who recruited 194 patients with primary knee osteoarthritis for a recent study "Chondroitin can slow the long-term progression of knee osteoarthritis while matching the symptom relief of celecoxib" which was presented at American College of Rheumatology 2015 Annual Meeting has found.
- Due to its classification as a dietary supplement, most companies in the US do not meet the prescription purity and other quality parameters outlined in the EP and BP.
- Most chondroitin products on the market contain glucosamine derived from shellfish which pose a problem to people who suffer from shellfish allergies.
- Only two companies in the US manufacture a chondroitin product that meets the EP of which only one offers a chondroitin only format which takes away the allergen and potential diabetes risk that glucosamine containing products have.
- Clinical studies have not identified any significant side effects or overdoses of chondroitin sulfate, which suggest its long-term safety. The Task Force of the European League Against Rheumatism (EULAR) committee recently granted chondroitin sulfate a level of toxicity of 6 in a 0-100 scale, confirming it is one of the safest drugs for osteoarthritis. Moreover, its safety is supported by an absence of drug-drug (chondroitin sulfate is not metabolized by cytochrome P450), and the lack of safe alternatives for patients multi-medicated for osteoarthritis and other accompanying diseases, e.g. diabetes, hypertension, hyperlipidemia, etc.

- The Cochrane Review Published on January 28th, 2015, which consisted of 43 studies with 9,110 people, concluded:
  - Chondroitin may improve pain slightly in the short-term (less than 6 months);
  - Chondroitin improves knee pain by 20% in slightly more people;
  - Chondroitin probably improves quality of life slightly as measured by Lequesne's index (combined measure of pain, function, and disability);
  - Chondroitin has little or no difference in adverse and serious adverse events versus other agents; and
  - Chondroitin slightly slows down the narrowing of joint space on X-rays of the affected joint.

- A pharmacoeconomic analysis by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) produced a consensus statement that provides "evidence in support of pharmacological interventions "with symptomatic slow-acting drugs for osteoarthritis (SYSADOAs, including chondroitin sulfate), in terms of management of OA pain and function, avoidance of adverse events, disease-modifying effects and long-term outcomes," including delay of total joint replacement surgery, and pharmacoeconomic factors such as reduction in healthcare resource utilization.

References:

Visit www.osteosyn.com/research for review and download full text of select studies listed below

Bishnoi M, Jain A, Hurkat P, Jain SK, Chondroitin sulphate: a focus on osteoarthritis Glycoconjugate Journal 19 May 2016 pp 1-13

Mantovani V, Maccari F, Volpi N. Chondroitin Sulfate and Glucosamine as Disease Modifying Anti-Osteoarthritis Drugs (DMOADs) Curr Med Chem. 2016; 23(11):1139-51.

Raynauld JP, Pelletier JP, Abram F, Delorme P, Martel-Pelletier J. Long-term effects of glucosamine/chondroitin sulfate on the progression of structural changes in knee osteoarthritis: 6-year follow-up data from the osteoarthritis initiative. Arthritis Care Res (Hoboken). 2016 Feb 16. DOI: 10.1002/acr.22866

Hochberg MC, Martel-Pelletier J, Monfort J, Möller I, Castillo JR, Arden N, Berenbaum F, Blanco FJ, Conaghan PG, Doménech G, Henrotin Y, Pap T, Richette P, Sawitzke A, du Souich P, Pelletier JP; MOVES Investigation Group. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. Ann Rheum Dis. 2016 Jan;75(1):37-44.

Provenza JR, Shinjo SK, Silva JM, Peron CR, Rocha FA. Combined glucosamine and chondroitin sulfate, once or three times daily, provides clinically relevant analgesia in knee osteoarthritis. Clin Rheumatol. 2015 Aug;34(8):1455-62.

Singh JA, Noorbaloochi S, MacDonald R, Maxwell LJ. Chondroitin for osteoarthritis. Cochrane Database of Systematic Reviews 2015, *Issue* 1. *Art. No.: CD005614. DOI: 10.1002/14651858.CD005614.pub2.*

Bruyere O, Cooper C, Pelletier JP, Maheu E, Rannou F, Branco J, Brandi M, Kanis J, Altman R, Hochberg M, Martel-Pelletier J, Reginster J. A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis--From evidence-based medicine to the real-life setting. Seminars in Arthritis and Rheumatism, Elsevier, 2015.

Purvis L, Carter E, Morin P Impact of the Medicare Hospital Readmission Reduction Program on Hospital Readmissions Following Joint Replacement Surgery, AARP Public Policy Institute, Oct 2015

Martel-Pelletier J, Farran A, Montell E, Vergés J and Pelletier J, Discrepancies in Composition and Biological Effects of Different Formulations of Chondroitin Sulfate, *Molecules* 2015, 20, 4277-4289; doi:10.3390/molecules20034277

Zhang W, Giancaspro G, Adams K, Neal-Kababick J, Hildreth J, Li A, Roman M, Betz J Electrophoretic Separation of Alginic Sodium Diester and Sodium Hexametaphosphate in Chondroitin Sulfate that Interfere with the Cetylpyridinium Chloride Titration Assay, Journal of AOAC International Vol. 97, No. 6, 2014

Fardellone P, Zaim M, Saurel AS, Maheu E. Comparative efficacy and safety study of two chondroitin sulfate preparations from different origin (avian and bovine) in symptomatic osteoarthritis of the knee. Open Rheumatol J. 2013; 7:1-12.

Schneider H, Maheu E, Cucherat M. Symptom-modifying effect of chondroitin sulfate in knee osteoarthritis: a meta-analysis of randomized placebo-controlled trials performed with structum® Open Rheumatol J. 2012; 6:183–9.

Pavelka K, Coste P, Géher P, Krejci G. Efficacy and safety of piascledine 300 versus chondroitin sulfate in a 6 months treatment plus 2 months observation in patients with osteoarthritis of the knee. Clin Rheumatol. 2010; 29:659–70.

Jordan KM; Recommendations Arden NK. EULAR (2003), "an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT)". *Ann Rheum Dis* ***62*** *(12): 1145–1155.* doi:10.1136/ard. 2003.01174

Volpi N Oral bioavailability of chondroitin sulfate (Condrosulf ®) and its constituents in healthy male volunteers, Osteoarthritis and Cartilage (2002) 10, 768–777

Bourgeois P, Chales G, Dehais J, Delcambre B, Kuntz JL, Rozenberg S. Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3 x 400 mg/day vs placebo. Osteoarthritis Cartilage. 1998; 6 (Suppl A):25–30.

Bucsi L, Poor G. Efficacy and tolerability of oral chondroitin sulfate as a symptomatic slow-acting drug for osteoarthritis (SySADOA) in the treatment of knee osteoarthritis. Osteoarthritis Cartilage. 1998; 6 (Suppl A):31–6

Morreale P, Manopulo R, Galati M, Boccanera L, Saponati G, Bocchi L. Comparison of the anti-inflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. J Rheumatol. 1996; 23:1385–91.

Thilo G, A Study of 35 Cases of Arthrosis Treated with Chondroitine Sulphuric Acid, Schweiz. Rundschau Med. (PRAXIS) 66 (1977)

Synutra Pure, Ltd.
2275 Research Blvd., Suite 500
Rockville, MD 20850
301-840-3888
800-601-8827 toll-free
www.osteosyn.com
www.synutrapure.com
Email contact: members@osteosyn.com