

Glucosamine and Chondroitin Sulfate and Osteoarthritis Food Advisory Committee: Petition Summaries

Two health claim petitions were submitted to FDA. One petition was submitted on behalf of Weider Nutrition International, Inc. (petitioner A) and the other was submitted on behalf of Rotta Pharmaceutical, Inc. (petitioner B). The claims concerned the relationships between the consumption of: (1) glucosamine and/or chondroitin sulfate and reduction in the risk of: osteoarthritis; joint degeneration; and cartilage deterioration (petitioner A), and; (2) crystalline glucosamine sulfate and a reduced risk of osteoarthritis (petitioner B). The following is a brief synopsis of the scientific data provided in the petitions, and the conclusions reached by the petitioners. This synopsis is of the petitions alone and does not include any FDA conclusions. The petitions can be found in the appendix of the briefing book.

I. Synopsis of Petitions (Note: Letters “A” and “B” preceding reference numbers correspond to the citations from petitioner A (Weider Nutrition International, Inc.) and petitioner B (Rotta Pharmaceutical, Inc.), respectively.)

A. Substance

Glucosamine is a glycoprotein derived from marine exoskeletons or produced synthetically. It is sold as the sulfate sodium chloride (sulfate) salt, hydrochloride (HCL) salt and N-acetyl-glucosamine. It is an endogenous substance that is required for the synthesis of glycoproteins, glycolipids, and glycosaminoglycans (also known as mucopolysaccharides). These carbohydrate-containing compounds are found in tendons, ligaments, cartilage, synovial fluid, mucous membranes, structures in the eye, blood vessels, and heart valves.

Chondroitin sulfate belongs to a class of very large molecules called glucosaminoglycans (GAGs), which are made up of glucuronic acid and galactosamine. Chondroitin is manufactured from natural sources, such as shark and bovine cartilage. Pure chondroitin is a relatively large molecule, weighing about 16,900 daltons. The species or tissue of origin, and the extraction method used, can affect the size of the molecule.

B. In vitro mechanistic data

Studies in human and animal primary cell cultures, established cell culture models, and tissue/organ cultures have reported various biochemical effects following exposure to glucosamine sulfate, glucosamine hydrochloride (HCl), and chondroitin sulfate. Preliminary research suggests that glucosamine affects cytokine-mediated pathways regulating inflammation and cartilage degradation and immune responses. Glucosamine seems to inhibit interleukin 1-beta (IL-1 β), thereby reducing inflammation and cartilage degradation (A113/B8, A132, A133, A134, A135, A136, A137, A138/B10, A139). Glucosamine reportedly stimulated proteoglycan synthesis, which may also be through inhibition of IL-1 β (A14, A113B8, A132, A133, A138/B10, A140/B9, A142, A143, A144, A148, A149). In addition, glucosamine reportedly possesses immunomodulatory activity (A150, A151) and has been reported to be a substrate for and stimulate new chondroitin sulfate synthesis (A113/B8, A147).

Chondroitin sulfate has been reported to stimulate production of proteoglycans (A142, A153, A155, A156, A157) and prevent cartilage degradation (A153, A159, A165, A166, A172), possibly via inhibition of IL-1 β (A153, A158). Reports also suggest a role for chondroitin sulfate

Glucosamine and Chondroitin Sulfate and Osteoarthritis Food Advisory Committee: Petition Summaries

in prevention of inflammation (A137, A160, A161) and immunomodulation (A131, A165, A166, A167, A168, A169, A170).

C. Animal models of OA

Dietary glucosamine sulfate has been reported to reduce kaolin- and adjuvant-induced tibio-tarsal arthritis in rats (A141) and glucosamine-HCL, with and without chondroitin sulfate, was reported to reduce cartilage degradation in a rabbit model of OA (A219). Consumption of glucosamine-HCL has been reported to enhance the rate of new articular cartilage proteoglycan synthesis in mice (A144). Diets supplemented with chondroitin sulfates have been reported to prevent articular cartilage degradation induced by chymopapain in rabbits (A162), Freund's adjuvant in mice (A163) and in a rabbit surgical instability model of OA (A219).

D. Human clinical studies

1. Mitigation of Symptoms

Relief of OA symptoms has been reported in OA patients taking glucosamine hydrochloride, glucosamine sulfate, chondroitin sulfate, and combination products of glucosamine plus chondroitin sulfate. The majority of the studies are on glucosamine sulfate relieving the symptoms of knee OA. Studies lasting from a few weeks to three years have reported that oral glucosamine sulfate/hydrochloride, chondroitin sulfate and their combination products can significantly improve symptoms of pain and functionality indices in patients with osteoarthritis (A111/B36, A173, A176/B25, A178/B32, A179/B26, A180/B16, A181/B15, A182/B31, A185/B34, A186/B29, A192, A193, A196, A197, A205, A206, A207, A208, A211, A212, A213, A218, A220/B48, A221/B47, A227, A228/B28, B27). Relief of OA symptoms by glucosamine and chondroitin sulfate has been compared with the non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen (A184/BB33, A185/B34, A186/B29, A187/B46), diclofenac sulfate (A208) and naproxen (A215).

2. Joint Degeneration and Cartilage Deterioration

Radiographic evidence suggests that glucosamine sulfate and chondroitin sulfate may slow joint degeneration in patients with osteoarthritis. OA patients taking glucosamine sulfate for up to three years had significantly less knee joint degeneration, less joint space narrowing, and significant symptom improvement when compared with placebo (A180/B16, A181/B15). Progression of knee joint space narrowing was reportedly prevented in OA patients taking chondroitin sulfate for one to three years when compared with placebo (A194, A207) or baseline (A193, A205, A206).

Compared with placebo, consumption of chondroitin sulfate for three years did not prevent development of OA in finger joints that were non-affected at the start of the study, but a significant decrease in the number of patients with new "erosive" OA finger joints was reportedly observed (A198). In a separate two year study, chondroitin sulfate plus naproxen did not prevent development of OA in finger joints that were non-affected at the start of the study, but compared with naproxen alone, a significant decrease in the number of joints with new erosions was reportedly observed (A215).

Investigators have reported biochemical evidence from OA patients that chondroitin sulfate may protect against cartilage and bone degradation. Compared with placebo, one year treatment of

Glucosamine and Chondroitin Sulfate and Osteoarthritis Food Advisory Committee: Petition Summaries

OA patients with chondroitin sulfate was reported to decrease markers of bone metabolism (serum osteocalcin, urine pyridinoline/deoxypyridinoline) and cartilage metabolism (serum keratin sulfate, cartilage oligometric matrix protein¹ (COMP)) (A193, A205). Compared with pre-treatment levels, short term treatment (5- 10 days) with chondroitin sulfate elevated synovial fluid proteoglycan and hyaluronic acid levels and decreased collagenolytic activity, phospholipase A2 and N-acetylglucosaminidase (A119/B49, A131).

II. Petitioners' Conclusions (see Appendix for copies of the petitions)

A. Petitioner A (Weider Nutrition International, Inc.)

The following conclusions are found on page 23 of petitioner's Exhibit 1 (scientific summary) submitted by petitioner A.

1. Maintaining the structural and functional integrity of the proteoglycan component of the extracellular matrix of articular cartilage is required for preservation of healthy joint architecture and biomechanics.
2. Imbalanced metabolism favoring catabolism within the extracellular matrix of articular cartilage produces degenerative changes in the proteoglycan composition of the matrix.
3. Compromise of the structural and functional integrity of the proteoglycan component of the extracellular matrix of articular cartilage results in net loss of articular cartilage tissue, inferior biomechanical competence and structural deformation of joint architecture.
4. Net degradation of the extracellular matrix of articular cartilage, accompanied by the production of spontaneous repair matrix with abnormal proteoglycan composition, results in asymptomatic subclinical osteoarthritic change.
5. The progression of degenerative asymptomatic osteoarthritic change to osteoarthritis is not inevitable.
6. The progression of degenerative osteoarthritic change is required in order for abnormalities in articular cartilage composition and structure to progress to osteoarthritis.
7. Osteoarthritic change in the absence of joint pain represents a modifiable risk factor for later development of osteoarthritis.
8. Dietary supplementation with D-glucosamine, glucosamine-HCL, glucosamine sulfate or chondroitin sulfate contributes to the preservation of articular cartilage, inhibits the initiation of osteoarthritic change in articular cartilage and inhibits the progression of osteoarthritic change to symptomatic osteoarthritis.
9. Dietary supplementation with D-glucosamine, glucosamine-HCL, glucosamine sulfate or chondroitin sulfate is an effective modifier of osteoarthritic change and reduces the risk for osteoarthritis.

B. Petitioner B (Rotta Pharmaceutical, Inc.).

The following conclusions are found on pages 5 and 45 of the petition.

“The scientific evidence in this Petition convincingly establishes that crystalline glucosamine sulfate, when given to individuals diagnosed with osteoarthritis, can prevent further joint degradation, can reverse the symptoms by minimizing the inflammation and restoring articular cartilage, can reduce joint pain and can result in increased joint function. Given the physiological mechanism of action of crystalline glucosamine sulfate and other factors, there also are sufficient data

¹ Not clearly identified as serum or urine COMP levels.

**Glucosamine and Chondroitin Sulfate and Osteoarthritis Food Advisory Committee:
Petition Summaries**

demonstrating the ability of crystalline glucosamine sulfate to be effective in reducing the risk of developing osteoarthritis.” (page 5)

“The preventative effects of crystalline glucosamine sulfate in this patient population with “mild osteoarthritis,” a patient population very similar to the “healthy population,” combined with the well-known mechanism of action for crystalline glucosamine sulfate support the ability of crystalline glucosamine sulfate to be effective in preventing the onset of osteoarthritis.” (page 45)