Use of crystalline glucosamine sulfate in osteoarthritis

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Osteoarthritis is the most common form of arthritis and the most prevalent among rheumatic diseases. It is a degenerative joint disorder with minimal signs of inflammation, which may affect all diarthrodial joints and whose most appropriate definition combines a description of the pathology of the disease with pain that occurs with joint use [1]. Osteoarthritis is particularly frequent at the large, weight-bearing joints of the lower limbs. Radiographic osteoarthritic changes of the knee tibiofemoral compartment occur in 5–15% of the general population aged 35–74 years in the Western world [2]. Symptomatic knee disease occurs in approximately 6% of US adults over 30 years of age [3], with general incidence and prevalence increasing two- to ten-fold from age 30 to 65 years [4]. The impact on disability attributable to knee osteoarthritis is similar to that due to cardiovascular disease and greater than that caused by any other medical condition in the elderly [5].

Treatment guidelines for knee and hip osteoarthritis have been developed by both the American College of Rheumatology (ACR) [6] and the EUROpean League Against Rheumatism (EULAR) [7,8]. The two guidance documents have been developed by different procedures and, although they share some basic principles, differ with respect to the level of recommendation of specific classes of drugs. This is particularly evident for SYmptomatic Slow Acting Drugs in OsteoArthritis (SYSADOA), the class of agents in which the drug focussed on in this review is generally included, and might be due to the differences in the regulatory status between the USA and Europe. For this and other reasons, the guidelines may soon need further updates.

Both guidelines suggest that acetaminophen (paracetamol) should be the oral analgesic used initially and, if successful, the preferred long-term symptomatic agent [6–8]. Nevertheless, this pure analgesic is less effective than nonsteroidal anti-inflammatory drugs (NSAIDs) in short-term pain relief [9]. On the contrary, recent meta-analyses suggest that the efficacy of NSAIDs in osteoarthritis is not great and, in particular, their long-term use is not supported by available data [10].

Therefore, there is a need for medications that offer acceptable short-term symptom control, but in particular have a role in the medium- and long-term management of disease (symptom-modifying effect), including the possibility to delay the progression of joint structure changes (structure-modifying effect), thereby affecting the evolution of the disease and thus preventing clinically significant disease outcomes (disease-modifying effect). These aims might be achieved by drugs that, unlike unspecific symptomatic agents, might exert specific effects on osteoarthritis pathogenesis factors. To date, glucosamine sulfate is probably the drug with the most extensive evidence in this regard.

Glucosamine sulfate
Glucosamine is a naturally occurring monosaccharide and a normal constituent of glycosaminoglycans in the cartilage matrix and...
synovial fluid [11]. However, it also exerts specific pharmacological effects on osteoarthritic cartilage and chondrocytes. Glucosamine base must be salted for pharmaceutical use, and glucosamine sulfate is the salt that was originally developed as a prescription drug and used in the vast majority of osteoarthritis clinical trials. However, some recent generic over-the-counter products and in particular a number of dietary supplements may contain glucosamine hydrochloride, whose treatment effects are much less well characterized, as will be discussed. In addition, several dietary supplements have appeared that claim glucosamine sulfate content, but that may be different from the prescription product described below.

For these reasons, the present review will concentrate on the crystalline glucosamine sulfate formulation that has been approved as a prescription drug in Europe and elsewhere, and that is available as a branded dietary supplement in the USA. Nevertheless, high-quality clinical trials conducted with glucosamine hydrochloride or other glucosamine sulfate formulations will also be reviewed, and their results analyzed to assess the overall evidence available for the use of glucosamine in osteoarthritis. In this respect, it must be noted that a recent Cochrane Review identified major differences in the results of clinical trials conducted with the glucosamine sulfate prescription formulation described here and those of studies conducted with other glucosamine preparations which failed to demonstrate a similar efficacy [12].

**Chemistry**

Crystalline glucosamine sulfate (Dona®, Viartril-S®, Arthryl®, Xicil® or other trademarks by the originator company Rottapharm, Monza, Italy), is also known as glucosamine sulfate sodium chloride. It is a pure substance (molecular weight [Mw]: 573.31) synthesized from chitin of sea origin and in which glucosamine (Mw = 179.17), sulfate, chloride and sodium ions are present in stoichiometric ratios of 2:1:2:2 (Figure 1). Glucosamine sulfate (Mw = 456.43) does not appear to be stable, unless prepared as crystalline glucosamine sulfate according to this patented process [13]. The dose is expressed as the net content in glucosamine sulfate and, as a prescription drug, the substance is most widely available as sachets of powder for oral solution of 1500 mg glucosamine sulfate to be administered once daily.

At present, it is unclear how other preparations of glucosamine sulfate, mainly available in countries where the substance is regulated as a dietary supplement, compare with this prescription formulation in terms of active ingredient content, purity and stability, since this information is generally not available. When formulations are unknown, and especially in view of the absence of appropriate bioequivalence studies (see ‘Pharmacokinetics and metabolism’ section), it is not known how the clinical efficacy and safety results obtained with crystalline glucosamine sulfate apply to these uncontrolled nutraceutical or generic preparations, and vice versa.

**Pharmacodynamics**

Glucosamine is preferentially incorporated by chondrocytes into the components of glycosaminoglycan chains in intact cartilage [14]. It stimulates the synthesis of physiological proteoglycans [15–17] and decreases the activity of catabolic enzymes in the cartilage, including matrix metalloproteases (MMPs) [17,18]. The compound is effective in vivo in experimental animal models of osteoarthritis [19,20]. For several years, the dominant belief was that most of the activities and the mechanism of action of glucosamine sulfate might be reconducted to the mere incorporation of glucosamine in glycosaminoglycans and, thus, the stimulation of their synthesis as a simple building block. However, this hypothesis appears to be over-simplified. In fact, while metabolic effects, especially if exerted at the level of the articular cartilage, might support a long-term joint structure-modifying activity, they may hardly explain the relatively short-term symptom-modifying effects outlined in clinical trials. Unsurprisingly, recent studies have demonstrated that glucosamine concentrations that are able to stimulate glycosaminoglycans synthesis in vitro are high [21] and probably largely in excess of those that may be achieved in biological fluids after oral administration to humans [22].

On the other hand, selected in vitro models illustrated that glucosamine might be metabolically effective at concentrations 100-fold lower and compatible with those found in biological fluids during treatment in humans [17]. In addition, the compound may selectively cumulate in the cartilage after repeated dosing, thereby possibly providing higher local concentrations [23]. An alternative hypothesis has been proposed that suggests looking for glucosamine metabolic activities in tissues where extracellular glucosamine concentrations should be higher, including the intestine, liver and kidney, and might modulate the compound anti-arthritic effects [24]. However, this hypothesis appears to be premature at present.
Glucosamine sulfate – DRUG EVALUATION

A unifying hypothesis for the compound mechanism of action in osteoarthritis has recently been proposed and supports the role of glucosamine sulfate as both a symptom- and structure-modifying agent in osteoarthritis. This mechanism refers to glucosamine-induced reversal of the pro-inflammatory and joint-degenerating effects of interleukin (IL)-1 [18,25,26]. More specifically, it inhibits the cytokine intracellular signaling cascade, namely the activation of the nuclear factor (NF)-κB pathway [27]. In particular, glucosamine sulfate has been shown to inhibit the IL-1-induced activation and nuclear translocation of active NF-κB family members in human osteoarthritic chondrocytes [28]. Via this mechanism, glucosamine sulfate was able to inhibit the gene expression and protein synthesis of cyclooxygenase (COX)-2, selectively over COX-1, thereby preventing the release of prostaglandin (PG)E2 in the culture media [28].

Several new evidences are progressively appearing to further substantiate this mechanism of inhibiting IL-1-induced expression of genes involved in the pathophysiology of joint inflammation and tissue destruction. NF-κB activity is inhibited by glucosamine sulfate at the level of both chondrocytes and synoviocytes, with a concomitant decrease in COX-2 protein synthesis, PGE2 release and, in chondrocytes, nitric oxide release, with a pattern that differs from that of other potential anti-osteoarthritic agents and NSAIDs [29]. Moreover, glucosamine sulfate consistently decreased IL-1-induced MMP synthesis in both type of cells, while NSAIDs tended to further increase their production [29].

Most of these in vitro experiments used glucosamine concentrations that were higher than those found in human plasma after therapeutic doses (see ‘Pharmacokinetics and metabolism’), which is common in mechanistic studies. However, recent studies indicated that this mechanism is operative at glucosamine concentrations of approximately 10 µM or lower [30], specifically, the concentrations found in human plasma or synovial fluid after therapeutic doses of crystalline glucosamine sulfate. Effective glucosamine concentrations (expressed as IC50) that inhibit IL-1-stimulated gene expression of different pro-inflammatory or proteolytic transcripts have been reported to range between 6.2 and 13.8 µM for IL-1 itself, MMP-3, COX-2 and inducible nitric oxide synthase [30].

Another recent study confirmed that, in vitro, glucosamine inhibits gene expression in the osteoarthritic cartilage [31]. Since glucosamine inhibits both anabolic and catabolic genes, the authors speculate that the therapeutic effects as a potential disease-modifying agent might be due to anticatabolic activities, rather than anabolic activities. Interestingly, they also found that glucosamine sulfate is a stronger inhibitor of gene expression than glucosamine hydrochloride [31], which may help to explain the different findings of recent clinical trials with different glucosamine salts and formulations, along with the recent human pharmacokinetic findings.

The differences between glucosamine sulfate and glucosamine hydrochloride might be important at both the pharmacological and pharmacokinetic levels, with sulfate concentrations increasing after administration of glucosamine sulfate [32,35]. This might possibly overcome a deficiency in inorganic sulfur caused by low levels of dietary proteins (containing sulfur amino acids) in the elderly. Sufficient sulfur is essential for the synthesis of proteoglycans and other sulfur-containing metabolic intermediates (e.g., coenzyme A and glutathione) that are important for chondrocyte metabolism [32,33].

**Pharmacokinetics & metabolism**

For a long period, limited knowledge about glucosamine pharmacokinetics (including oral bioavailability, peak plasma levels and tissue distribution) hampered the full understanding of the relationships between the compound clinical effects and its mechanism of action. In addition, the inability to document the compound pharmacokinetics and, thus, to perform bioequivalence studies against the patented formulation of crystalline glucosamine sulfate approved as a prescription drug in continental Europe and elsewhere, favored the appearance on the market of other undocumented glucosamine salts (e.g., hydrochloride), improperly stabilized glucosamine...
sulfate substances, different dosage forms or regimens, whose clinical trial results were clearly less favorable (as will be reviewed later).

The main limitation for the description of glucosamine pharmacokinetics has been the lack of suitable biochemical methods with sufficient sensitivity and specificity for the detection of the compound in biological fluids. Early studies tried to elucidate the pharmacokinetics and metabolism of oral glucosamine sulfate in rats, dogs and humans, using \(^1\text{C}\)-labeled glucosamine [23]. Although these studies provided compelling information about the absorption, distribution and elimination of radioactivity, they were not fully able to differentiate the unchanged drug from its metabolites and/or degradation products. When tentative specific methods for the determination of glucosamine in human plasma were developed, they were not suitably sensitive to monitor the plasma concentrations of the unchanged compound after oral administration of therapeutic doses [23].

More recent investigations into different forms of oral glucosamine in rats [34], dogs [35] and horses [36] had to use doses much higher than those used therapeutically in humans owing to the high limit of quantization of the assays employed, and their relevance to the treatment of osteoarthritis is at least questionable. Nevertheless, the serum and synovial fluid concentrations of glucosamine have been determined in horses with reasonable assay sensitivity, after single-dose administration of glucosamine hydrochloride at what the authors designated ‘human clinically relevant’ doses, although they failed to use an allometric scale to calculate such doses and, therefore, their results are difficult to interpret [24]. Nevertheless, maximal glucosamine concentrations in plasma were similar to those later described in humans [22,37]. Conversely, the concentrations in the synovial fluid were at least tenfold lower [24].

A very preliminary study in patients with variously localized osteoarthritis found glucosamine plasma levels up to 11.5 \(\mu\)M, 1.5–3 h after ingestion of a single 1500 mg dose of glucosamine sulfate. Although these peak plasma levels were in line with those found in correct human pharmacokinetics studies [36], they were not reached in all patients, possibly due to protocol limitations, as acknowledged by the authors themselves [22].

The complete pharmacokinetic profile of glucosamine has lately been described by Persiani and colleagues, after repeated administrations (i.e., at steady state) of the standard crystalline glucosamine sulfate formulation, (1500 mg once daily), to healthy volunteers in a rigorously designed pharmacokinetics study [37]. These authors have developed and validated a liquid chromatography method with mass spectrometry detection (LC-MS/MS) that has a very low limit of quantitation [37]. This enabled them to detect endogenous plasma glucosamine concentrations with distinct intrasubject variability, and to study the pharmacokinetics of the exogenously administered compound with higher precision. They found that glucosamine is rapidly bioavailable from orally administered crystalline glucosamine sulfate, with maximum average plasma concentrations up to 100-fold higher than endogenous levels and in the 10 \(\mu\)M range after approximately 3 h. Steady-state pharmacokinetics parameters indicate that glucosamine distributes to both the vascular and extravascular compartments and is eliminated with a half-life estimated to be approximately 15 h, thus supporting once-daily dosing. Absolute bioavailability could not be assessed in this study, but was estimated to be approximately 25% with the help of other recent animal data [38].

Preliminary knee osteoarthritis patient data from the same group indicate the presence of endogenous glucosamine levels in both plasma and synovial fluid, with distinct intrasubject variability (particularly at the level of the latter), whose possible pathophysiological significance should be further investigated [39]. In these patients, repeated once-daily doses of 1500 mg crystalline glucosamine sulfate reached similar peak plasma and synovial fluid concentrations, with an almost 1:1 relationship, which were also in the 10 \(\mu\)M range [39]. These data are different from those described in horses [24] and call attention to possible species-specific differences and/or on the precision of the assays employed, which appears to be higher in the studies by Persiani and colleagues [37,39]. Interestingly, the 10 \(\mu\)M concentration range found in human plasma and synovial fluid [21,37,39] is effective on chondrocytes \textit{in vitro} in the inhibition of IL-1-induced gene expression [50]; specifically, the putative mechanism of action of glucosamine in osteoarthritis. Conversely, the same concentrations are probably insufficient to stimulate cartilage glycosaminoglycan synthesis [21,22]. This finding would suggest abandoning this latter over-simplified hypothesis.
Single-dose pharmacokinetic studies with other glucosamine formulations at the same unit dose of 1500 mg. such as the glucosamine hydrochloride solid preparation used in the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) (see later), found glucosamine peak concentrations in plasma that were only 3 µM [40], that is, at least threefold lower than the steady-state concentrations reached with 1500 mg of crystalline glucosamine sulfate, and they might be even lower when the 1500 mg daily dose is fractioned; for example, as 500 mg three-times daily, as in GAIT. These lower concentrations found with glucosamine hydrochloride are less effective in vitro on the putative mechanism of action of glucosamine described earlier [30].

Unfortunately, there are no pharmacokinetics and bioavailability studies of other glucosamine sulfate preparations and, therefore, it is impossible to comment on their clinical value relative to the prescription formulation.

Clinical efficacy
The putative mechanism of action, described above, supports the role of glucosamine sulfate as both a symptom- and structure-modifying drug in osteoarthritis.

All clinical trials performed until the end of 2004 have been systematically evaluated in a recent Cochrane review [12], which supersedes two previous high-quality meta-analyses [41,42]. This Cochrane review considered the results of all 20 eligible randomized controlled trials (RCTs) available at that time with any glucosamine formulation for symptom modification and concluded that glucosamine was superior to placebo for improvement in both pain and function, with a moderate effect size. However, these results were driven by the ten RCTs that evaluated the prescription formulation of crystalline glucosamine sulfate object of this review (labeled 'Rotta preparation' in the Cochrane review) and which found a high effect size for pain and a moderate effect size for function relative to placebo. Pooled results for trials using a different glucosamine preparation failed to reach statistical significance when compared with placebo.

Only high-quality trials conducted with any glucosamine formulation will be considered in this review. Given the different results outlined in the Cochrane Review, trials of prescription crystalline glucosamine sulfate are the main subject of this review, and they will be reported separately from studies performed with other formulations.

High-quality trials of crystalline glucosamine sulfate can be classified based on their treatment duration and aims.

Short-term trials of glucosamine sulfate for symptom relief
Besides placebo-controlled trials, four short-term studies compared the prescription glucosamine sulfate formulation with an NSAID, and found it superior in two and equivalent in two, for treatment periods between 4 and 12 weeks [12].

One of the studies that better describes the short-term, symptom-modifying effect of glucosamine sulfate versus both placebo and NSAIDs has been published in abstract form [43]. Based on the complete data and information largely reported below, the Cochrane review established that this study had adequate allocation concealment and the highest rated methodological quality for both study design and analysis [12]. This was a randomized, double-blind, placebo- and active-controlled trial on four parallel groups of patients, with mono- or bilateral primary knee osteoarthritis, according to the ACR criteria. Patients (a total of 319; 75% females) had an average age of 65.5 years, a mean body mass index (BMI) of 27.8, and a history of daily knee pain and function limitation requiring medical treatment for at least the previous 6 months. After wash-out from previous symptomatic medications, they were randomly assigned to once-daily treatment for 12 weeks with either 1500 mg glucosamine sulfate powder for oral solution, one 20 mg piroxicam capsule, the combination of both glucosamine sulfate and the NSAID, or double placebo, according to a double-dummy technique to preserve blindness in all groups. At the end of the 12 weeks, treatments were withdrawn and patients followed-up for a further 8 weeks. Acetaminophen (paracetamol) 500 mg tablets were provided for rescue analgesia as needed, and their use recorded on a patient daily diary. All groups were comparable for demographic and baseline disease characteristics, the latter being of moderate severity. Figure 2 reports the change in the primary parameter represented by the Lequesne index, whose final outcome is reported in Table 1. Both glucosamine sulfate and piroxicam demonstrated a distinct trend for improvement over placebo, evident already after 2 weeks of treatment and similar for the two drugs up to 4 weeks. As listed in Table 1, this behavior was superimposable to that demonstrated in previous 4-week placebo-controlled [44] or NSAID-controlled [45] trials. After
4 weeks, the improvement with glucosamine sulfate continued slightly more steadily than with piroxicam (Figure 2, left) and was superior at the end of the 12-week treatment course. The combination of glucosamine sulfate with the NSAID tended to exhibit an insignificant faster symptomatic effect over the first 15 days of treatment. Thereafter, the improvement was indistinguishable from that of glucosamine sulfate alone. Over the 8 weeks of follow-up after drug withdrawal, the patients previously receiving piroxicam tended to lose most of the effect formerly achieved (Figure 2, right and Table 1). Conversely, the previous beneficial effect was long-lasting in patients who had received glucosamine sulfate alone or in combination with the NSAID. Recourse to paracetamol for rescue analgesia in this trial was occasional and variable, with minimal average consumption (<1–2 tablets/day) in a similar proportion of patients, without significant differences between groups. Long-term trials for disease modification & new trials for the management of disease symptoms Glucosamine sulfate should not be regarded as a drug for short-term symptom relief, but one for osteoarthritis disease management. This includes symptom modification over appropriate treatment durations, specifically at least 6 months according to current regulatory guidelines [46], and possibly long-term trials for both joint structure modification and symptom modification (i.e., true disease modification). Three pivotal trials currently satisfy these requirements for crystalline glucosamine sulfate.

Reginster and colleagues [47] and Pavelka and colleagues [48] were the first to demonstrate a putative disease-modifying effect by a pharmacological agent in two long-term studies. In these 3-year, randomized, placebo-controlled clinical trials, they were able to demonstrate that glucosamine sulfate was not only able to control the symptoms of the disease over such a
Table 1. Mean change in the Lequesne algo-functional index from baseline in crystalline glucosamine sulfate high-quality trials of different treatment durations.

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<tbody>
<tr>
<td></td>
<td>Placebo n = 120</td>
<td>GS n = 121</td>
<td>Placebo n = 77</td>
<td>GS n = 79</td>
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<tr>
<td>Baseline</td>
<td>10.6 ± 3.5</td>
<td>10.6 ± 3.6</td>
<td>10.4 ± 3.0</td>
<td>10.3 ± 3.0</td>
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<tr>
<td>Change from baseline 4 weeks</td>
<td>-2.3 (-2.9 to -1.7) p = 0.037 vs placebo</td>
<td>-3.2 (-3.9 to -2.6)</td>
<td>-2.9 (-3.5 to -2.2) p &lt; 0.001 vs placebo</td>
<td>-4.5 (-5.2 to -3.7) p &lt; 0.001 vs placebo</td>
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<td>p &lt; 0.001 vs placebo</td>
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<td>12 weeks</td>
<td>-0.7 (-1.4 to -0.1)</td>
<td>-4.8 (-5.4 to -4.2)</td>
<td>-2.9 (-3.5 to -2.2)</td>
<td>-4.5 (-5.2 to -3.7)</td>
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<tr>
<td>6 months</td>
<td></td>
<td></td>
<td>p &lt; 0.001 vs placebo</td>
<td>p &lt; 0.001 vs placebo</td>
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<td>3 years</td>
<td></td>
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<td>NS vs combination</td>
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Intention-to-treat (ITT) approach by the last observation carried forward, except in Pavelka [48] where a worst-case scenario was employed. The lower row reports the mean change from the end of treatment scores, after drug withdrawal, in the only study where this assessment was performed (see also Figure 2), with an ITT approach on all treatment period completers, assuming return to baseline values for early withdrawals. Statistical analysis by analysis of variance, with correction for multiple comparisons by Dunnett pairwise comparisons in Herrero-Beaumont [58], or by the Tukey test, after covariating on baseline and end-of-treatment scores, respectively, in Rovati [43]. Two high-quality trials could not be included in this table: the study by Müller-Fassbender [45] versus ibuprofen for using a modified version of the Lequesne index and whose results for GS at 4 weeks are superimposable to those of Noack [44] and not different from those obtained for ibuprofen 1200 mg/day; the long-term placebo-controlled study by Reginster [47] for using the WOMAC index only and whose results at 3 years are superimposable to those of Pavelka [48] who used the WOMAC index as a secondary end point.

Data are mean ± SD for baseline scores and mean with 95% confidence interval for changes.

*Combination of glucosamine sulfate + piroxicam.

GS: Glucosamine sulfate; NS: Not significant; SD: Standard deviation; WOMAC: Western Ontario and McMaster osteoarthritis index.
long-term treatment course, but could also significantly decrease the progression of joint structure changes in patients with mild-to-moderate osteoarthritis of the knee. The data were particularly strong in the subgroup of female postmenopausal patients [49].

Joint structure changes were principally assessed by monitoring radiographic joint space narrowing. The results are summarized in Table 2 and illustrate a similar quantitative effect in the two trials, as previously acknowledged [42]. Reservations have been expressed that these results were obtained with the full extension knee radiographic view, a technique that, although state-of-the-art at the time of the trials, might be less efficient than newer semiflexed views, and the results might have been biased by the marked symptom improvement by glucosamine sulfate [48]. In fact, improvement in pain might improve the degree of knee extension and artificially increase the tibiofemoral joint radiographic space, by changing the medial tibial plateau alignment with the x-ray beam [50]. However, it has recently been demonstrated that pain was not a confounder in joint space narrowing assessment in these trials [51].

Indeed, the long-term symptom-modifying effect in the two long-term trials was termed ‘impressive’ [52]. Other reports have questioned the significance of this symptom improvement [53]; however, this has been recently reassessed and found to be clinically relevant [54], although the effect size is small due to the mild symptom characteristics of the patients at enrolment.

In addition, preliminary follow-up data of these patient cohorts suggest that, on average, 5 years after the end of the two long-term trials and drug withdrawal, the patients who had received glucosamine sulfate were less likely to undergo total joint replacement [55,56]. If confirmed, these data would indicate that glucosamine sulfate might indeed affect the progression of osteoarthritis, preventing clinically significant disease outcomes. This finding might be explained by the symptom- and structure-modifying effect achieved during the treatment period, in terms of clinically relevant response. In particular, a recent position paper suggested that ‘failure’ to treatment might be a good predictor of joint surgery and a proper surrogate outcome during long-term clinical trials for disease modification in osteoarthritis [57]. When this group of experts assessed the proportion of ‘failures’, defined as a joint space narrowing of at least 0.5 mm, and less than 20% improvement in the Western Ontario and MacMaster OA Index (WOMAC) pain subscale, in the two long-term studies by Reginster and colleagues and by Pavelka and colleagues, they found that there were 41% failures overall with glucosamine sulfate versus 60% on placebo (p = 0.003) [57].

The most recent pivotal study assessed the role of glucosamine sulfate in the management of knee osteoarthritis symptoms over 6 months in comparison with placebo and with a reference drug represented by acetaminophen (paracetamol) [58]; in other words, the preferred long-term symptomatic medication indicated by current osteoarthritis practice guidelines [6,7]. The Glucosamine Unum In Die (once-a-day) Efficacy (GUIDE) trial evaluated 318 patients (88% women) randomized to double-dummy placebo, or 1 g acetaminophen tablets three-times daily, or to the standard prescription formulation of glucosamine sulfate soluble powder 1500 mg once daily (hence the acronym of the study). The data reported in Table 1 illustrate that the mean improvement in the Lequesne index with glucosamine sulfate was significantly higher than with placebo. Conversely, the improvement with acetaminophen failed to reach statistical significance versus placebo. The clinical relevance of the effect size of glucosamine sulfate on the primary outcome in

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<th>Study (sample size)</th>
<th>Enrolment JSW</th>
<th>3-year JSN</th>
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<tr>
<td></td>
<td>Placebo</td>
<td>GS (mean ± SD; mm)</td>
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<tr>
<td>Reginster (n = 106,106)</td>
<td>3.95 ± 1.24</td>
<td>3.82 ± 1.32</td>
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<tr>
<td>Pavelka (n = 101,101)</td>
<td>3.63 ± 1.57</td>
<td>3.89 ± 1.48</td>
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*p = 0.003 and ‡p = 0.001 versus placebo.

CI: Confidence interval; GS: Glucosamine sulfate; JSW: Joint space width; JSN: Joint space narrowing; SD: Standard deviation.
this trial is witnessed by the higher proportion of treatment responders according to the Osteoarthritis Research Society (OARSI-A) criteria: 39.6% versus 21.2% with placebo (p = 0.007). Acetaminophen also had more responders than placebo, although at a lower degree of significance (33.3%; p = 0.047).

These results suggest that glucosamine sulfate might be the preferred symptomatic medication in knee osteoarthritis vis a vis current practice guidelines, if employed at the standard dose regimen of the prescription formulation of this and the previously described pivotal trials. On the other hand, these results are at odds with those of the National Institutes of Health (NIH)-supported GAIT study, where the glucosamine-treated group demonstrated only a nonsignificant trend of efficacy [59]. This large, 6-month trial compared glucosamine, given as dietary supplement glucosamine hydrochloride 500 mg three-times daily or chondroitin sulfate, or their combination, with placebo and with celecoxib as a reference standard. The overall results might be clouded by the huge placebo effect (60%), and by an insufficiently controlled use of the rescue analgesic medication, since even the reference standard medication produced disappointing, although statistically significant, efficacy results compared with placebo [60]. Conversely, none of the supplements was significantly superior to placebo [59]. Glucosamine hydrochloride at the dose of 500 mg three-times daily was used only in one previous RCT whose results were mostly negative [61]. Indeed, the editorial accompanying the GAIT study states that the NIH finding for glucosamine is not surprising, given the nonconventional glucosamine formulation used, since all previous favorable trials have been conducted with the glucosamine sulfate prescription preparation [62]. As described in the 'Pharmacodynamics' and 'Pharmacokinetics' sections earlier, the peak glucosamine plasma levels achieved with the NIH hydrochloride formulation are much lower [40] than with the prescription sulfate formulation used in GUIDE [37,39] and, therefore, they might not share the same pharmacological properties [30]. In addition, sulfates have been suggested as an important component of the glucosamine mechanism of action [32]. Interestingly, the most significant results in GAIT were achieved in a subgroup analysis in more severe patients when glucosamine hydrochloride was combined with chondroitin sulfate [59], presumably increasing the sulfate plasma levels [33], if not even those of glucosamine metabolites, to concentrations closer to those achieved with the prescription glucosamine sulfate formulation used in GUIDE and the other pivotal trials.

Overall assessment of the symptom-modifying effect of crystalline glucosamine sulfate in both short- & long-term clinical trials Table 1 demonstrates a coherence of results for symptomatic improvement with glucosamine sulfate over short-to-medium-term treatment courses ranging from 4 weeks to 6 months [43–45,58]. The magnitude of the effect also appears to be comparable, with the exception of one trial where it is higher mainly due to a lower placebo response [43].

In the trials where a comparison with a non-specific symptomatic medication is performed, glucosamine sulfate might provide similar symptom relief after the first 2–4 weeks [43,45] and it might lean towards superiority in studies of 3–6 months duration [43,58], including a persistent effect after drug withdrawal, compared with a progressive loss of effect, for example, with NSAIDs [45].

In the long-term trial by Pavelka that used the Lequesne index as the primary symptom outcome, the effect size relative to placebo on this parameter is similar to that observed in shorter trials [48], as suggested by the data in Table 1 and as acknowledged by the Cochrane review [12]. Few published trials of crystalline sulfate used the WOMAC index as a symptom outcome (i.e., only the long-term trials of Reginster [47] and Pavelka [48]), and reported a significant difference on the total index and on both pain and function subscales. While the difference on the total index is clearly clinically relevant, the Cochrane review indicates that the standardized mean difference for WOMAC pain and function is not significant, suggesting an effect size that might not be clinically relevant [12]. However, when the effect size is calculated according to the standard formula (Table 3), it is statistically significant for both parameters in both trials, again with a coherence of results between the two. The effect size is small (i.e., between 0.20 and 0.50), but this is not surprising in long-term, 3-year, placebo-controlled trials in patients with mild disease characteristics. In addition, this effect size is of the same magnitude as that of NSAIDs for their preferential application, in other words, over short-term treatment courses [10]. Therefore, it confirms that glucosamine sulfate may be an appropriate agent for the long-term management of knee osteoarthritis.
severe patient subgroups [59]. It suggests potentially higher efficacy in more glucosamine hydrochloride at a low unit dose, with all limitations deriving from the use of hand, the subgroup analysis of the GAIT study, damage [63]. Conversely, structure modification is achieved irrespective of baseline joint structure in the long-term trials [47,48] to moderate-severity, ranging from mild-to-moderate symptoms in patients with different baseline of view, effective symptom modification can be observed in patients with different baseline severity, ranging from mild-to-moderate symptoms in the long-term trials [47,48] to moderate-to-severe in shorter studies [43–45]. On the other hand, the subgroup analysis of the GAIT study, with all limitations deriving from the use of glucosamine hydrochloride at a low unit dose, suggests potentially higher efficacy in more severe patient subgroups [59].

Subanalyses from the long-term studies by Reginster [47] suggest that symptom modification is achieved irrespective of baseline joint structure damage [63]. Conversely, structure modification appears to be more effective in patients with milder joint changes when treatment is started [64].

Clinical studies conducted with other glucosamine formulations

The GAIT study is among the most important trials performed with glucosamine and is the largest [59]. Its negative results have been summarized earlier. Unfortunately, it has been conducted with glucosamine hydrochloride at the dose of 500 mg three-times daily, specifically with a substance, formulation and dose that are different from those of the prescription glucosamine sulfate used in all latest trials, and whose different pharmacokinetic, and probably pharmacodynamic, patterns have been discussed previously. In addition, the high placebo response and the diverging findings in the disease severity subgroup analysis have raised several questions [60], and an opportunity has probably been lost to clarify some of glucosamine clinical effects in a large and independent trial [62].

GAIT appears at least to confirm that glucosamine hydrochloride given at a dose of 500 mg three-times daily might not be a preferred option, as previously suggested by Houp [61]. In this latter study, a formulation and dose of glucosamine hydrochloride, similar to that used in GAIT, produced only limited and nonsignificant benefit over placebo on the symptoms of knee osteoarthritis in a relatively small group of 101 patients treated for 8 weeks. Therefore, it is not known if glucosamine hydrochloride is as effective as glucosamine sulfate in the treatment of osteoarthritis [12].

However, three high-quality trials of glucosamine sulfate have been published that were not able to replicate the favorable effects on symptom modification that have been described in the previous sections of this review [65–67]. All these trials used dietary supplement glucosamine sulfate preparations whose purity and stability are not described, since these are not prescription products. In addition, nothing is known about the bioavailability of the active ingredient, glucosamine, relative to the prescription formulation: this would be an essential prerequisite of any generic product, before any comparison can be made with the reference standard. The lack of this information is indeed surprising. Finally, most of the preparations used in these trials fractioned the total daily dose in two or three administrations, and this may further decrease the active ingredient peaks in plasma and other biological fluids that have been demonstrated to be effective in vitro [30].

In a 6-month, randomized, double-blind, placebo-controlled study, Hughes and Carr tested a glucosamine sulfate formulation never tested previously (potassium chloride glucosamine sulfate, plus vitamin C, calcium carbonate and manganese) in a small cohort of heterogeneous patients with differing knee osteoarthritis severity [65]. Almost 50% of them were taking NSAIDs at

| Table 3. Effect size of glucosamine sulfate versus placebo on WOMAC pain and function. |
|---|---|---|
| Outcome | GS effect size (95% CI) | Ref. |
| **WOMAC pain** | | |
| Reginster | 0.27 (0.002–0.54) | [48] |
| Pavelka | 0.30 (0.03–0.58) | [48] |
| Two studies pooled | 0.27 (0.08–0.46) | |
| **WOMAC function** | | |
| Reginster | 0.32 (0.05–0.59) | [47] |
| Pavelka | 0.32 (0.04–0.60) | [48] |
| Two studies pooled | 0.31 (0.11–0.50) | |

Effects are calculated after 3 years in long-term trials of Reginster [47] and Pavelka [48]. Effect sizes have been calculated with their 95% CI according to the standard method with bias correction by Hedges (1985), as the difference between the mean change from baseline for the verum and placebo groups, divided by the pooled SD. Results are presented separately for the two studies and, after standardizing the results on a 0–100 mm VAS, for the two studies pooled. CI: Confidence interval; GS: Glucosamine sulfate; OA: Osteoarthritis; SD: Standard deviation; VAS: Visual analog scale; WOMAC: Western Ontario and Macmaster OA index.

To date, no demographic characteristics have been identified that enable the prediction of which patients will benefit from the administration of glucosamine sulfate. From a clinical point of view, effective symptom modification can be observed in patients with different baseline severity, ranging from mild-to-moderate symptoms in the long-term trials [47,48] to moderate-to-severe in shorter studies [43–45]. On the other hand, the subgroup analysis of the GAIT study, with all limitations deriving from the use of glucosamine hydrochloride at a low unit dose, suggests potentially higher efficacy in more severe patient subgroups [59].
cosamine sulfate has been described, similarly this study design is very interesting, glu-
over 6 months after randomization. Although disease flare between glucosamine and placebo 
There were no differences in the incidence of symptoms after both short- [43] and long-term 
osteoarthritis, to produce a carry-over effect on other symptomatic slow-acting drugs in 
fered with the added evaluation of glucosamine effectiveness, also given the inclusive eligibility 
criteria, the unbalanced randomization for several baseline characteristics and the lack of 
direct patient observation, as discussed by the authors [66].

Cibere and colleagues conducted a placebo-controlled discontinuation trial in a small 
group of 137 current users of glucosamine sup-
ments who had reported at least moderate improvement in knee osteoarthritis pain [67]. 
There were no differences in the incidence of disease flare between glucosamin 
placebo over 6 months after randomization. Although this study design is very interesting, glu-
cosamine sulfate has been described, similarly to other symptomatic slow-acting drugs in 
osa-arthritis, to produce a carry-over effect on symptoms after both short- [43] and long-term 
clinical use [55,56], which may confound the assessments in a discontinuation trial. In fact, 
almost 60% of patients did not relapse during the 6-month observation period in this study. 
In addition, the baseline characteristics were imbalanced between groups, with an over-
whelming majority of male patients and a more severe disease in the glucosamine group. 
Finally, since patients were required to remain on the dose of glucosamine that they were tak-
ing before the study, 35–40% of patients were randomized to a dose of 1000 mg/day or less, 
while all successful clinical trials have been performed with a dose of 1500 mg of glucosamine 
sulfate.

Given these limitations in study design and the use of noncharacterized glucosamine prepa-
rations, it is not clear how this clinical trial experience should be considered in the assess-
ment of glucosamine efficacy in osteoarthritis. As a minimum and in agreement with the find-
ings of the Cochrane Review, it is suggested that there may be differences in efficacy 
between the prescription formulation of crystalline glucosamine sulfate and dietary sup-
plement glucosamine preparations. Safety was good in all these clinical studies.

Safety & postmarketing surveillance
All studies and meta-analyses have recognized the good overall safety profile of glucosamine sulfate 
and of glucosamine in general. Table 4 reports the proportion of patients with adverse events in the 
most important short-term clinical trials and in pivotal long-term trials of crystalline glucosamine 
sulfate (with the exclusion of the GUIDE study, whose complete results are currently unpublished). 
Withdrawals due to adverse events, lack of efficacy or other reasons are also reported. 
There were never statistically or clinically significant differences between glucosamine sulfate and 
placebo in the incidence of adverse events or of safety-related withdrawals. On the other hand, in 
comparative trials, the incidence of adverse events and related withdrawals was always signifi-
cantly higher in the reference groups receiving conventional NSAIDs than in the glucosamine 
sulfate group, with the majority of adverse events in the NSAID-treated patients being obviously 
referred to the gastrointestinal tract.

Although at a significantly lower incidence than with conventional NSAIDs, the low propor-
tion of adverse events with glucosamine sulfate are related to the gastrointestinal system and consist 
of mild and transient abdominal pain, nausea, dyspepsia, diarrhea or constipation. Headache, 
drowsiness and fatigue have also been reported. Uncommon adverse events are represented by 
depressed mood, vertigo and skin rash. With regard to the latter, cross-reactions in patients with 
seafood allergy are unlikely, due to the purification process that excludes the presence of protein 
residues in the starting material of sea origin.

Overall, the incidence of these adverse events taken together is lower than 15% in the princi-
pal short-term studies, as shown in Table 3. In the pivotal trials of Reginster and colleagues [47] and 
Pavelka and colleagues [48], the long-term exposure implies a higher incidence of adverse 
events, which is nevertheless identical to that of placebo and has the same pattern as that sum-
marized above. In these long-term studies, musculoskeletal events were also reported, but 
they are probably related to the primary rheu-
matic condition. Cardiovascular events were also common in this elderly population, but 
they were not related to the study medication and major events occurred with an incidence 
similar to placebo [69].
Glucosamine is an amino monosaccharide that can enter the hexosamine pathway (one of the alternative routes of glucose metabolism) and thereby increases insulin resistance, as suggested by animal experimental studies using suprapharmacological intravenous doses of the compound [70]. Although this remains an area of attention, human studies with extremely high intravenous [71] or even intra-arterial [72] glucosamine doses indicated that such a mechanism is probably not operating in humans, where insulin sensitivity, secretion or action were not affected. More recently, a study in healthy volunteers with oral repeated doses of a glucosamine sulfate formulation at 1500 mg daily, demonstrated no changes in serum insulin or blood glucose levels with 3-h glucose tolerance test [73]. Another placebo-controlled study showed that patients with Type 2 diabetes receiving a glucosamine and chondroitin sulfate combination for 3 months had no change in their diabetes management, or in hemoglobin A1c concentrations [74]. Finally, fasting plasma glucose levels were not modified in former short-term studies with crystalline glucosamine sulfate, as well as in the long-term trial by Reginster [75], while in the 3-year study by Pavelka, four patients developed diabetes during the study, but three were on placebo and only one on glucosamine sulfate [48]. Other laboratory evaluations never detected significant abnormalities in hematological or other metabolic parameters.

Interactions with other drugs are unlikely, since glucosamine is mainly absorbed via glucose transporters and does not compete for general absorption mechanisms; in addition, it is mainly metabolized independently of the cytochrome P450 enzyme system [76].

Since crystalline glucosamine sulfate is a prescription drug in several countries of the world, it is subject to strict postmarketing surveillance.
ar or l e.

and pharmacological behavior, may have played previously undocumented glucosamine salts (i.e., other factors described above, such as the use of with consequent differences in pharmacokinetic hydrochloride), at different dose regimens and therefore might be a disease-modifying agent the drug has joint structure-modifying properties in clinical trials. Two 3-year trials also suggested that use is largely supported by different high-quality short- and long-term treatment courses, whose line glucosamine sulfate to these other preparations date back to the year 2000 [6], in other words, prior to the most intriguing new evidence, and classify the compound among the experimental agents, the EULAR guidelines for knee osteoarthritis [7] attribute to glucosamine sulfate the highest level of evidence, 1A, and the highest strength of recommendation, A, for the management of disease symptoms, along with only six out of the 34 pharmacological and non-pharmacological treatment modalities considered [7]. Conversely, the evidence at the level of the hip is still scanty [8].

The pharmacological events that support the clinical effects of glucosamine sulfate in osteoarthritis appear to be related to the inhibition of the IL-1 intracellular signaling pathway and, thus, of cytokine-induced gene expression. These pharmacological effects are achieved in vitro at drug concentrations found in plasma and synovial fluid of knee osteoarthritis patients after oral administration of the standard therapeutic doses. Differences in the clinical effects with generic or dietary supplement glucosamine hydrochloride formulations may indeed be related to differences in dose regimens and in pharmacokinetics, which may lead to differences in the pharmacological properties. In addition, the presence of sulfates in the prescription drug formulation, which is stabilized according to a patented process, has also been suggested to be important from the point of view of favoring some of the compound pharmacometabolic characteristics, which might not be shared by glucosamine hydrochloride. Conversely, preparations of glucosamine sulfate, other than the prescription formulation, manifest differences in quality and dose regimens that would require appropriate pharmacokinetic and bioequivalence assessment [78]. Since this is not currently available, it is impossible to apply the efficacy and safety results obtained with crystalline glucosamine sulfate to these other preparations and vice versa, as already noted in the recent Cochrane review [12].
Future perspective

Glucosamine sulfate is the first pharmacological agent for which a combined symptom- and structure-modifying effect has been demonstrated in appropriate long-term clinical trials. While this evidence is still unique within the treatment of osteoarthritis, future studies of new drugs should take into account this experience and the evolving technology in outcome measurement and clinical trial performances.

Symptoms of the disease will need to be assessed over appropriate treatment durations, in other words, for at least 6 months and for the duration necessary to evaluate joint structure changes, if any. The clinical relevance of the symptom change should be determined based on appropriate patient-reported outcomes.

To date, joint structure-modifying activity has been evaluated mainly by plain radiography, quantitatively monitoring joint space narrowing as a surrogate for cartilage loss and adopting a qualitative assessment for bone reactive changes. More recent radiographic techniques are emerging to assess these outcomes with more accuracy and precision, and must be adopted in clinical trials after their validation is completed. In the meantime, other imaging techniques may prove more powerful in detecting cartilage quantitative and qualitative changes, as well as the modifications in other joint structures and tissues: the best candidate technique in this respect is magnetic resonance imaging.

Whichever technique is employed, changes in joint structure should be clinically relevant in terms of their association with favorable symptom outcomes or by modifying the natural history of the disease. In addition, long-term trial outcomes should focus on parameters of patient’s disability, quality of life and disease management. The latter should prospectively assess a possible decrease in the recourse to surgical total joint replacement, once this evaluation can be standardized, and focus on appropriate pharmacoeconomic evaluations.

Besides the general remarks above, future studies of glucosamine sulfate might explore the effects of the substance when administered by the parenteral route, either systemically (e.g., by the intramuscular route), or locally (i.e., intra-articularly), despite the good oral bioavailability reviewed here. In addition, the potential of combination therapy with other drugs, either symptomatic medications or potential disease-modifying agents, deserves further attention.

Finally, glucosamine sulfate has been studied mainly in clinical trials of primary osteoarthritis. Anecdotal evidence of efficacy in secondary osteoarthritis, including post-traumatic disease or sport injury and rehabilitation, has been reported and would require confirmation in appropriately designed studies. Given its putative mechanism of action, the potential of the compound in the prevention of osteoarthritis might also be investigated.

Executive summary

Chemistry
- Crystalline glucosamine sulfate is the stabilized form of glucosamine sulfate, specifically, the glucosamine salt used as a prescription drug in osteoarthritis.
- Glucosamine, sulfate, chloride and sodium ions are present in stoichiometric ratios of 2:1:2:2.
- Other glucosamine salts (e.g., hydrochloride) and substances are widely used as dietary supplements, and may not share the same properties.

Mechanisms of action
- Different in vitro studies demonstrated that glucosamine sulfate has both anabolic properties (stimulating the synthesis of proteoglycans) and antiprotective activities (inhibiting the effects of enzymes, such as metalloproteases).
- However, the mere incorporation of the aminosugar in glycosaminoglycans and stimulation of their synthesis as a simple building block is unlikely, due to the high concentrations required.
- The substance mechanism of action appears to be rather due to glucosamine-induced reversal of the pro-inflammatory and joint-degenerating effects of interleukin (IL)-1.
- This effect is probably accomplished by inhibition of the cytokine intracellular signaling pathways, namely the activation of nuclear factor (NF)-κB.
- Indeed, glucosamine sulfate inhibits IL-1-stimulated gene expression of cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), cytokines and metalloproteases at glucosamine concentrations found in human plasma (10 µM) and synovial fluid after administration of glucosamine sulfate at standard oral doses.
- Sulfate may contribute to the mechanism of action of glucosamine sulfate, overcoming a possible deficiency in inorganic sulfur in the elderly. This provides an additional mechanism compared with other glucosamine salts (e.g., hydrochloride), besides a possibly different pharmacokinetic behavior.
Executive summary

Pharmacokinetic properties

- Following oral administration of crystalline glucosamine sulfate 1500 mg once daily in humans, peak plasma concentrations of approximately 10 µM glucosamine are achieved after 3 h on average.
- Similar levels are achieved in the synovial fluid of knee osteoarthritis patients.
- The terminal elimination half-life from human plasma is approximately 15 h.
- Glucosamine absolute bioavailability from crystalline glucosamine sulfate is estimated to be approximately 25% from animal data.
- Glucosamine hydrochloride provides glucosamine peak plasma levels in humans that are threefold lower than 1500 mg once-daily glucosamine sulfate and may be less pharmacologically effective.
- Glucosamine is metabolized independently of the cytochrome P450 system.

Clinical efficacy

- The efficacy of crystalline glucosamine sulfate in the short-term (4–12 weeks) control of osteoarthritis symptoms versus placebo, of at least comparable magnitude to conventional nonsteroidal anti-inflammatory drugs (NSAIDs) and with a long-lasting effect after drug withdrawal, has been shown in different clinical studies, including three principal trials in patients with moderate-to-severe symptoms.
- Three pivotal, placebo-controlled trials demonstrated a statistically significant and clinically relevant symptom-modifying effect for treatments ranging from 6 months to 3 years in knee osteoarthritis patients with mild-to-moderate disease.
- The two pivotal, long-term, 3-year trials demonstrated a joint structure-modifying effect based on radiological joint space narrowing.
- In the pivotal 6-month trial (Glucosamine Unum In Die (once-a-day) Efficacy study [GUIDE]), a comparator group receiving the currently preferred symptomatic medication acetaminophen failed to reach a significant benefit versus placebo, differently from glucosamine sulfate.
- In the 6-month, NIH-sponsored Glucosamine/Chondroitin Arthritis Intervention Trial, glucosamine hydrochloride 500 mg three-times daily failed to demonstrate the same efficacy of glucosamine sulfate 1500 mg once daily in GUIDE and in other previous trials, thereby highlighting possible differences in pharmacokinetic and pharmacological behavior.
- Similarly, studies performed with dietary supplement glucosamine sulfate preparations did not demonstrate the same efficacy of the prescription product.

Safety & tolerability

- In all clinical trials, glucosamine sulfate had an incidence of adverse events and related withdrawals similar to placebo.
- In comparative trials, safety was significantly better than that of conventional NSAIDs.
- The low proportion of adverse events consists mainly of mild and transient episodes of abdominal pain, nausea, dyspepsia, diarrhea, constipation, headache, drowsiness and fatigue. Uncommon adverse events are represented by depressed mood, vertigo and skin rash.
- Cross-reactions in patients with seafood allergy are unlikely, owing to the purification process that eliminates protein residues in the starting material of sea origin.
- Human studies failed to demonstrate an effect on glucose metabolism, although this remains an area of attention due to the possible interaction with the hexosamine pathway.
- Glucosamine sulfate is not expected to interact with other drugs (with rare exceptions), as it does not interfere with general absorption mechanisms and is not metabolized by the cytochrome P450 system.

Dosage & administration

- The most widely studied and approved prescription formulation is available as sachets of oral soluble powder of crystalline glucosamine sulfate, equivalent to 1500 mg glucosamine sulfate, to be administered once daily.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (★★) to readers.


• Practice guidelines including most of the trials performed in osteoarthritis, specifically at the knee joint, which are therefore evidence-based.

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Glucosamine sulfate – DRUG EVALUATION


• Clinical trial that reflects most of the results of previous studies of glucosamine sulfate for short-term symptom modification.


• Pivotal 3-year clinical trial demonstrating symptom and structure modification for glucosamine sulfate in knee osteoarthritis.


• Pivotal confirmatory 3-year trial, replicating the results of Reginster and colleagues (47).


• Demonstrates that pain relief by glucosamine sulfate did not confound the assessment of the compound structure-modifying effect identified in the trials of Reginster and Pavelka (47, 48).


• Position paper on the use of total joint replacement as an outcome in osteoarthritis clinical trials, summarizing some of the data of the two abstracts above that suggest that glucosamine sulfate might reduce the incidence of joint surgery.


• New pivotal trial of glucosamine sulfate for symptom modification in knee osteoarthritis.


• NIH-sponsored trial of glucosamine hydrochloride, which failed to demonstrate the same benefit on symptoms of trials of glucosamine sulphate.


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