







# **CRYSTALLINE GLUCOSAMINE SULFATE - CGS**

---

## Product Monograph

Copyright © 2009 Rottapharm|Madaus

Printed in Italy in May 2009

Layout and graphic design: Silvia Ghera

Johan & Levi Editore  
[www.johanandlevi.com](http://www.johanandlevi.com)

This book is protected by copyright. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means without the prior permission in writing of copyright holders and of the publisher.

Although great care has been taken in compiling the content of the publication, the publisher and its servants are not responsible or in any way liable for the currency of the information, for any errors, omission or inaccuracies, or for any consequences arising therefrom.

Provided as a service to the healthcare profession by Rottapharm|Madaus.

ISBN 978-88-6010-051-1

## INDEX

p. 9	<b>1. Summary of Key Concepts</b>
p. 13	<b>2. Osteoarthritis</b>
	2.1 Introduction
	2.2 Pathogenesis
	2.3 Guidelines for the Management of Osteoarthritis: The Key Role of Glucosamine
p. 21	<b>3. CGS - Chemistry and Pharmacy</b>
	3.1 CGS: a Unique Synthetic Process for a Unique Active Ingredient
p. 27	<b>4. CGS - Mechanism of Action and Pharmacology</b>
	4.1 Traditional Mechanisms of Action for Glucosamine
	4.2 The True Mechanism of Action of Crystalline Glucosamine Sulfate in OA
	4.3 <i>In vivo</i> Pharmacology
p. 33	<b>5. CGS - Pharmacokinetics</b>
	5.1 The Pharmacokinetics of Crystalline Glucosamine Sulfate in Humans
p. 41	<b>6. CGS - Clinical Efficacy in OA</b>
	6.1 Studies Designed to Assess the Efficacy of CGS as a Symptom-Modifying Drug in OA
	6.2 Pivotal Studies Designed to Assess the Efficacy of

CGS as a Structure-Modifying Drug in OA

- 6.3 Studies Derived from the Pivotal Long-Term Trials
- 6.4 Glucosamine Therapy for Treating Osteoarthritis: the Cochrane Review
- 6.5 Clinical Studies With other Glucosamine Products and Combinations

p. 67

## **7. CGS - Safety and Tolerability**

- 7.1 Safety in Short-Term Trials
- 7.2 Safety in Pivotal (Medium- and Long-Term) Trials
- 7.3 Reviews and Guidelines Assessing the Safety Profile of Glucosamine
- 7.4 Safety in Special Groups and Situations
- 7.5 Interactions With other Drugs and other Forms of Interaction

p. 81

## **8. CGS - Pharmacoeconomics**

- 8.1 Pharmacoeconomic Considerations Based on the Pivotal Long-Term Trials

p. 85

## **9. References**









## CHAPTER 1

# Summary of Key Concepts

- Osteoarthritis (OA) is the most common form of arthritis, and has an immense socioeconomic impact.
- In the EULAR guidelines for the management of OA, Glucosamine has been assigned the highest
  - level of evidence (1A),
  - strength of recommendation (A), and
  - quality score for the trials performed (24 out of a maximum of 28 points).
- The recent Osteoarthritis Research Society International (OARSI) guidelines recommend Glucosamine Sulfate, namely Crystalline Glucosamine Sulfate (CGS, Rottapharm), for treating OA. The reason for this specific recommendation is that the evidence for the efficacy of Glucosamine in OA is linked only to the trials conducted with CGS.
- Glucosamine base and Glucosamine Sulfate are unstable and cannot be used to prepare solid oral dosage forms. CGS is the stabilized form of Glucosamine Sulfate originally developed by Rottapharm and can be used to prepare solid oral dosage forms. Other Glucosamine preparations may differ from the original and have not been studied extensively. In addition, products sold as dietary supplements may not contain the amount of the substance written on the label.

- CGS inhibits IL–1-induced expression of inflammatory and matrix degradation markers at Glucosamine concentrations of 10  $\mu$ M or lower. Such concentrations are similar to those found in the plasma and synovial fluid of OA patients after repeated once daily administration of CGS at therapeutic doses. This mechanism supports both the symptom- and the structure-modifying effects of Glucosamine in OA, as long as the compound is formulated to reach the systemic circulation and the joint in sufficient concentrations.
- Other Glucosamine products and dosages produce significantly lower peak plasma concentrations than CGS 1500 mg once daily. Such lower concentrations might not reach the pharmacologically effective threshold. The combination of Glucosamine and chondroitin sulfate reduces the bioavailability of Glucosamine.
- CGS is the only form of Glucosamine that has been successful in clinical trials. The core of efficacy assessments for CGS is represented by the results of three pivotal trials, which support the favorable effects of Glucosamine on OA symptoms and progression.
- CGS 1500 mg once daily should be the preferred symptomatic medication for medium- and long-term treatments in patients with knee OA. In fact, CGS is at least as effective as acetaminophen—the preferred treatment in OA practice guidelines—in improving the symptoms associated with OA.
- Two pivotal 3-year trials have shown, for the first time, that a pharmacological intervention (CGS) can delay the progression of joint structure changes. According to regulatory requirements, combined symptom- and structure-modifying effects have been obtained in these two large, independent, placebo-controlled trials. This suggests that Glucosamine (in the form of CGS) may be the first disease-modifying agent in OA.
- The structure-modifying effects of CGS are clinically relevant because CGS decreases the incidence of total joint replacements. Patients with better preserved joint structure are those who benefit more

from the structure-modifying properties of CGS. This finding supports early intervention with CGS in OA.

- Glucosamine products other than CGS do not have symptom- or structure-modifying effects in OA. This finding is consistent with the results from mechanistic and pharmacokinetic studies. For instance, the peak Glucosamine plasma levels achieved with Glucosamine hydrochloride are lower than those reached with CGS and may not achieve the pharmacologically effective concentration.
- There is no clinical evidence, or rationale, to support combining Glucosamine with chondroitin sulfate. Moreover, chondroitin sulfate reduces the bioavailability of Glucosamine.
- CGS is a highly safe product. The incidence of adverse events and related withdrawals is similar to that of the placebo and significantly lower than that of NSAIDs. Therapeutic doses of CGS do not affect glucose metabolism. Moreover, because CGS does not interfere with absorption mechanisms and is not metabolized by the cytochrome P450 system, the potential for interaction with other drugs is very low.
- CGS 1500 mg once daily is a cost-effective treatment for OA. CGS compares favorably with both NSAIDs and placebo in pharmacoeconomic analyses.



## CHAPTER 2

# Osteoarthritis

### 2.1 Introduction

Osteoarthritis (OA) is the most common form of arthritis, and has a huge socioeconomic impact. Because its prevalence increases with age, OA will clearly become even more prevalent in the future <sup>1,2</sup>. It can occur in any joint but usually affects weight-bearing joints (knee, hip, and cervical and lumbosacral spine) and the hand joints that are involved in pincher grip. Osteoarthritis is commonly considered an organ disease, with important contributing factors possibly originating in different joint tissues, including subchondral bone and synovium. Particular attention has been devoted to the degeneration of articular cartilage as the primary event in the disease process. However, the precise pathogenetic mechanism (biomechanical, biochemical, or other) is still relatively unknown.

Osteoarthritis is a heterogeneous disease, the onset, pattern of joint involvement, and severity of which vary greatly <sup>3</sup>. The clinical features of osteoarthritis are symptoms – mainly pain and functional impairment (Table 1) – and pathological changes in joint structure. Unfortunately, these characterizing features are poorly correlated, especially in the early stages of the disease and throughout its development, although in the end both together are determinants of the disease and treatment outcome, represented by surgical joint replacement. Before that, the symptoms are the main factors in the management of patients, because the symptoms are respon-

sible for disability and impaired quality of life. For instance, the risk of disability attributable to knee OA (defined as needing help walking or climbing stairs) is similar to that caused by cardiovascular disease and greater than that due to any other medical condition in elderly persons <sup>1,4</sup>.

**TABLE 1.**

Common signs and symptoms of osteoarthritis

Signs	Symptoms
Crepitus	Pain
Restricted movement	Stiffness
Muscle wasting/weakness <ul style="list-style-type: none"> <li>• ± effusion, increased warmth</li> <li>• ± instability</li> </ul>	Functional impairment <ul style="list-style-type: none"> <li>• ± anxiety, depression</li> </ul>
Bony swelling	Alteration in shape
Deformity	—
Tenderness <ul style="list-style-type: none"> <li>• joint line</li> <li>• periarticular</li> </ul>	—

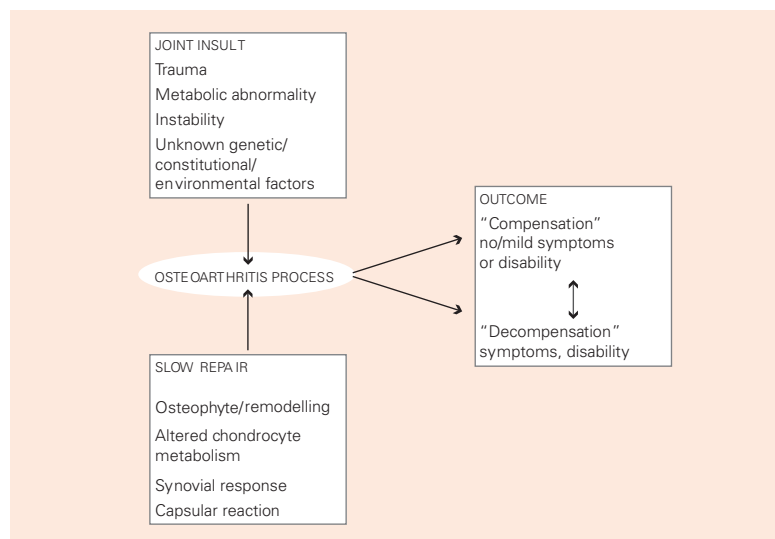
## 2.2 Pathogenesis

OA is increasingly viewed as a metabolically active, dynamic process involving both cartilage destruction and repair (Figure 1). OA can be triggered by biochemical changes as well as by mechanical injury, and all the tissues in the joint are involved in an adaptive response <sup>5,6,7,8</sup>. Cytokines, especially interleukin-1 (via intracellular mechanisms involving the transcription factor NF-κB), play a critical role in cartilage damage <sup>9,10</sup>. Increased metabolic activity in the cartilage, new bone formation, and remodeling of the joint may reverse tissue loss and redistribute mechanical forces across the damaged joint. In addition, joint stability may be maintained and possibly enhanced by capsular thickening. The outcome of the adaptive response will depend on the balance between the severity and chronicity of the injury and the effectiveness of repair mechanisms. In many cases the repair may rectify the adverse effects of the injury (compensated osteoarthritis), but in some cases severe injury or a poor tissue response may result in 'decompensated osteoarthritis', leading to symptoms, disability, and progressive structural damage <sup>5</sup>.

The molecular events involved in the development of osteoarthritis may occur long before the onset of symptoms<sup>78</sup>. Further characterization of these events will provide the diagnostic tools that are required to identify and monitor those patients at risk of developing the disease. In this way, it will be possible to act early with drugs that can modify the natural course of the disease, thus maximizing the benefits of treatment.

**FIGURE 1.**

Variable outcome of osteoarthritis as a repair process



## 2.3 Guidelines for the Management of Osteoarthritis: The Key Role of Glucosamine

The management of osteoarthritis requires chronic pharmacological and non-pharmacological approaches. The European Medicines Agency (EMA) has issued guidance on the clinical investigation of medicinal products used in the treatment of osteoarthritis (CPMP/EWP/784/97, adopted July 1998)<sup>11</sup>. Drugs for osteoarthritis have been classified as follows:

- **Symptom-modifying drugs** > These agents act on symptoms with no detectable effect on the structural changes of the disease
- **Structure-modifying drugs** > Based on their mechanism of action, these drugs are expected to have an effect on the progression of the pathological changes in osteoarthritis. Moreover, they may or may not have an independent effect on symptoms.

This classification is in agreement with that previously set forth in the recommendations of acknowledged scientific organizations, such as the Group for the Respect of Ethics and Excellence in Science (GREES) and the Osteoarthritis Research Society International (OARSI) <sup>12,13</sup>. Although no existing drug was classified as structure-modifying at the time of the recommendations/guidance above, all drugs currently approved for the treatment of osteoarthritis within the European Economic Area (EEA) may be classified as symptom-modifying, as long as they fulfill the requirements set forth in the CPMP document <sup>11</sup>. Indeed, the document does not consider it particularly fruitful to classify drugs that induce symptomatic relief as fast-acting [e.g., non-steroidal anti-inflammatory drugs (NSAIDs)] or slow-acting [e.g., drugs previously classified as Symptomatic Slow Acting Drugs for Treatment of Osteoarthritis (SYSADOA)] <sup>14</sup>.

Treatment guidelines for knee and hip osteoarthritis have been developed by both the American College of Rheumatology (ACR) <sup>15</sup> and the European League Against Rheumatism (EULAR) <sup>16,17</sup>. These guidance documents were developed following different procedures and, although they share some basic principles, they 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 Glucosamine is generally included, and might be due to the differences in regulatory requirements between the US and Europe.

Both American and European guidelines suggest that acetaminophen (paracetamol) is the oral analgesic to try first and, if successful, should be the preferred long-term symptomatic agent <sup>15,16,17</sup>. Nevertheless, this pure analgesic is less effective than NSAIDs in short-term pain relief <sup>18</sup>. On the other hand, recent meta-analyses suggest that NSAIDs are not greatly effective for osteoarthritis and, above all, that their long-term use is not supported by available data <sup>19</sup>.

Ideally, treatments for OA should

- offer acceptable short-term symptom control and have a role in the medium- and long-term management of the disease (**symptom-modifying effect**);
- delay the progression of joint structure changes (**structure-modifying effect**);



- modify the evolution of the disease and thus prevent clinically significant disease outcomes (**disease-modifying effect**).

These aims might be achieved by drugs that, unlike unspecific symptomatic agents, exert specific effects on pathogenetic mechanisms.

**TABLE 2.**

EULAR guidelines <sup>16</sup>: an evidence-based approach to the management of knee osteoarthritis. Final set of 10 recommendations based on both evidence and expert opinion

Glucosamine Sulfate is probably the drug with the most extensive evidence in this regard. The evidence-based EULAR practice guideline, which takes into account most of the trials carried out in osteoarthritis, sets Glucosamine Sulfate as one of the drugs with the highest quality score compared to acetaminophen, NSAIDs, and non-pharmacological therapies <sup>16</sup>. EULAR's ten final recommendations on the treatment of knee osteoarthritis are summarized in Table 2.

1. The optimal management of knee OA requires a combination of non-pharmacological and pharmacological treatment modalities.
2. The treatment of knee OA should be tailored according to:
  - (a) Knee risk factors (obesity, adverse mechanical factors, physical activity),
  - (b) General risk factors (age, comorbidity, polypharmacy),
  - (c) Level of pain intensity and disability,
  - (d) Signs of inflammation—for example, effusion,
  - (e) Location and degree of structural damage.
3. Non-pharmacological treatment of knee OA should include regular education, exercise, appliances (sticks, insoles, knee bracing), and weight reduction.
4. Paracetamol is the oral analgesic to try first and, if successful, should be the preferred long term oral analgesic.
5. Topical applications (NSAID, capsaicin) have clinical efficacy and are safe.
6. NSAIDs should be considered for patients unresponsive to paracetamol. In patients with an increased gastrointestinal risk, non-selective NSAIDs and effective gastroprotective agents, or selective COX 2 inhibitors should be used.
7. Opioid analgesics, with or without paracetamol, are useful alternatives in patients for whom NSAIDs, including COX 2 selective inhibitors, are contraindicated, ineffective, and/or poorly tolerated.
8. **SYSADOA (Glucosamine Sulfate, chondroitin sulfate, ASU, diacerein, hyaluronic acid) have symptomatic effects and may modify structure.**
9. Intra-articular injection of long acting corticosteroid is indicated for flare-ups of knee pain, especially if accompanied by effusion.
10. Joint replacement has to be considered in patients with radiographic evidence of knee OA who have refractory pain and disability.

In the EULAR guidelines for the management of knee OA<sup>16</sup>, Glucosamine was assigned the highest

**TABLE 3.**

Current EULAR guidelines<sup>16</sup>:  
level of evidence and  
strength of recommendation  
for some of the most used  
OA therapies

- level of evidence (1A),
- strength of recommendation (A),
- quality score for the trials performed (24 out of a maximum of 28 points), and
- among the highest effect sizes<sup>A</sup> (0.43-1.02; Table 3).

Treatment	Level of evidence	Strength of recommendation	Quality score*	Effect size**
Glucosamine	1A	A	24	0.43-1.02
Conventional NSAIDs	1A	A	17	0.47-0.96
Coxibs	1B	A	23	0.50
Acetaminophen/Paracetamol	1B	A	20	-
Education	1A	A	13	0.28-0.35
Exercise	1B	A	15	0.57-1.0

\* Median score on a 0-28 point scale addressing design, methodology, and statistical power of the studies performed;  
\*\* Range, if available

In September 2005, OARSI appointed an international committee of experts to produce consensus recommendations for the management of knee and hip OA. Recommendations were developed based on a critical appraisal of existing guidelines, a systematic review of research evidence, and a consensus opinion.

<sup>A</sup>. Effect size (ES) is the best, single indicator of the quantitative efficacy of an intervention vs. the comparator (placebo) and it is ideal in meta-analyses.

ES = (mean change\* active) – (mean change\* placebo)/pooled standard deviation

ES<0.20 = not clinically relevant

ES>0.20 = small †

ES>0.50 = moderate

ES>0.80 = large

Statistically significant if the 95% CI does not cross the 0 line

\*From baseline; †Usual outcome for OA interventions

These recommendations, published in 2007<sup>20</sup> and 2008<sup>21</sup>, are:

- up to date
- patient-focused
- evidence-based
- shared by Opinion Leaders worldwide.

OARSI current guidelines acknowledge that Glucosamine may provide both symptom- and structure-modifying benefits in the treatment of OA. Specific references have been made to the Crystalline preparation of Glucosamine Sulfate—i.e., the Rottapharm preparation—approved as a medicinal product for the treatment of OA in Europe, Asia and Latin America. The chemical differences between Crystalline Glucosamine Sulfate (CGS) and other Glucosamine salts and formulations are detailed in the next chapters. A summary of the consensus about the role of Glucosamine in the management of OA is given in Table 4.

**TABLE 4.**

OARSI recommendations for the management of hip and knee OA: focus on Glucosamine

Recommendations related to symptom-modifying effects	
1- Glucosamine in general	Treatment with Glucosamine may provide symptomatic benefits in OA patients.
2- Glucosamine Sulfate	Glucosamine Sulfate is recommended in 6/10 existing guidelines for the management of knee or hip OA.
3- Glucosamine Sulfate vs. Glucosamine hydrochloride	The effect size (ES) for trials using Glucosamine Sulfate was 0.44 (95% CI 0.18, 0.70) compared with 0.06 (95% CI -0.08, 0.20) for those using Glucosamine hydrochloride.
<b>4- Crystalline Glucosamine Sulfate (Rottapharm)</b>	<b>The ES for trials using the Rottapharm preparation of Glucosamine Sulfate was 0.55 (95% CI 0.29, 0.82) compared with 0.11 (95% CI -0.16, 0.38) for trials with other Glucosamine products.</b>
Recommendations related to structure-modifying effects	
1- Glucosamine in general	Treatment with Glucosamine may have structure-modifying effects in OA patients.
<b>2- Crystalline Glucosamine Sulfate (Rottapharm)</b>	<b>Evidence that Crystalline Glucosamine Sulfate 1500 mg once daily has structure-modifying effects in patients with knee OA comes from two placebo-controlled RCTs (conducted by Rottapharm), and two systematic reviews and meta-analysis.</b>

Nearly all the clinical trials summarized in this product monograph were performed in patients with osteoarthritis of the knee. In one trial, patients with osteoarthritis of the spine were enrolled. In accordance with the current EMEA/CPMP guidelines <sup>11</sup>, this improves the homogeneity of the patients studied. In addition, the guidance document states that compounds that have demonstrated efficacy either at hip or knee level will be registered for the treatment of osteoarthritis of the knee and the hip, i.e. without distinction between the large joints of the lower limbs.

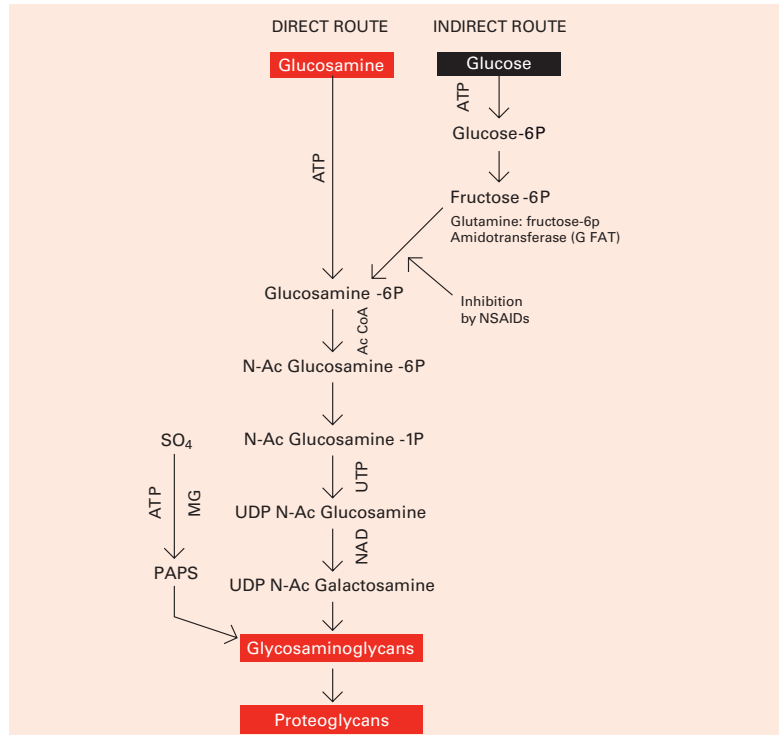
## CHAPTER 3

# Crystalline Glucosamine Sulfate Chemistry and Pharmacy

Glucosamine (molecular weight [MW]=179.17) is a naturally occurring monosaccharide (i.e., a derivative of glucose) and a normal constituent of glycosaminoglycans and proteoglycans in the cartilage matrix and synovial fluid <sup>22</sup> (Figure 2).

**FIGURE 2.**

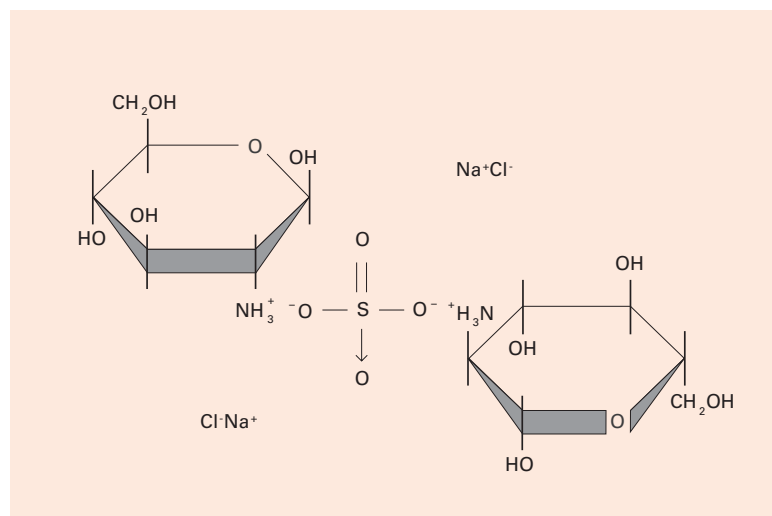
The biosynthetic pathway of glycosaminoglycans and proteoglycans



Glucosamine also exerts specific pharmacological effects on osteoarthritic cartilage. However, Glucosamine base must be salified for pharmaceutical use. Crystalline Glucosamine Sulfate (CGS, MW = 573.31; Figure 3) is the salt that was originally developed by Rottapharm and that was used, with positive results, in the vast majority of clinical trials on osteoarthritis.

**FIGURE 3.**

Chemical structure of Crystalline Glucosamine Sulfate (CGS; originally developed by Rottapharm)



Crystalline Glucosamine Sulfate has been approved as a prescription drug in Europe and elsewhere for the treatment of osteoarthritis and/or its symptoms. CGS is also marketed as a branded dietary supplement in the US. CGS is most widely available as sachets of powder for oral solution to be administered once daily. Each sachet contains 1884 mg of CGS, but the dose is commonly expressed as the net content of Glucosamine Sulfate (GS, 1500 mg). Rottapharm CGS is the only type of Glucosamine used successfully in clinical trials. Other types of Glucosamine widely available as dietary supplements or generics in different forms, namely:

- salts—e.g., Glucosamine hydrochloride (G-HCl)
- dosages—e.g., 500 mg three times daily, or
- combinations—e.g., with chondroitin sulfate

may not have adequate pharmacodynamic/pharmacokinetic/clinical trial support.

It is unclear how other preparations of Glucosamine Sulfate, mainly available in countries where the substance is regulated as a dietary supple-

ment, compare with CGS in terms of active ingredient content, purity, and stability. Indeed:

- such information is often not available
- some recent generic over-the-counter products and dietary supplements may contain Glucosamine hydrochloride, the clinical effects of which are much less characterized.

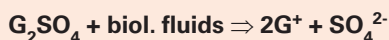
Moreover, because the content and purity of the various over-the-counter Glucosamine preparations differ markedly—from 41 to 108% of the mg content stated on the label<sup>23</sup>—their efficacy and safety may also vary markedly.

If Glucosamine is to be used as a therapeutic agent in OA, it is important that products conform to their label descriptions<sup>24</sup>. When formulations are unknown, especially in the absence of appropriate bioequivalence studies, it is not known how the clinical efficacy and safety results obtained with CGS apply to uncontrolled nutraceutical or generic preparations, and *vice versa*. Unfortunately, the data regarding most of these agents are negative, or at least conflicting, and unfairly cast doubts on the serious and consistent data that have been generated with CGS. In this respect, a recent Cochrane Review identified major differences between the results of clinical trials conducted with CGS and those of studies conducted with other Glucosamine preparations<sup>25</sup>. These are the main reasons why some pages of the present monograph have been devoted to clarifying what CGS is, how it is obtained, and why this active ingredient is unique.

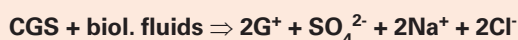
### 3.1 CGS: a Unique Synthesis Process for a Unique Active Ingredient

Glucosamine is a pure substance synthesized from chitin of marine origin. Chitin, the main component of crustacean shells, is a long-chain polymer of N-acetyl-Glucosamine. Glucosamine base and Glucosamine Sulfate (GS) are unstable unless prepared as Crystalline Glucosamine Sulfate (CGS) according to the unique patented process that is summarized below<sup>26</sup>.

- GS is an ionic substance. When dissolved in water or biological fluids, it gives a solution in which Glucosamine and sulfate ( $\text{SO}_4^{2-}$ ) ions are present in a stoichiometric ratio of 2:1



- Unfortunately, GS in the pure form is an extremely hygroscopic substance (i.e., it absorbs water). Because of this disadvantage, it cannot be used to prepare solid oral dosage forms.
- Rottapharm scientists devoted great effort to creating a stable form of GS. Eventually, a wet process was developed, which produced a mixed, crystalline, stable, and non hygroscopic salt (Glucosamine Sulfate Sodium Chloride). This product was called Crystalline Glucosamine Sulfate or, in an abbreviated form, CGS. When dissolved in water or biological fluids, CGS gives a clear solution in which Glucosamine, sulfate, chloride, and sodium ions are present in stoichiometric ratios of 2:1:2:2, according to the following scheme



- CGS has the same pharmacological and toxicological characteristics of GS. But unlike GS, GCS is stable and can be used to prepare solid oral dosage forms.
- Most other Glucosamine Sulfate products are prepared by simply mixing Glucosamine hydrochloride (G-HCl) and sodium or potassium sulfate. These mechanical mixtures do not assure homogeneity in the distribution of the ionic species in solution, with an unbalanced ratio between Glucosamine and sulfate ions.

#### CONCLUSIONS

**Glucosamine base and Glucosamine Sulfate are unstable and cannot be used to prepare solid oral dosage forms. CGS is the stabilized form of Glucosamine Sulfate, and is a unique active product ingredient that can be used to prepare solid oral dosage forms. CGS is obtained by a patented process and is the drug substance originally developed by Rottapharm. Other Glucosamine preparations may differ from the original and have not been studied extensively. In addition, products sold as dietary supplements may not contain the amount of the substance written on the label.**



CHAPTER 4

Crystalline Glucosamine Sulfate  
Mechanism of Action and Pharmacology

4.1 Traditional Mechanisms of Action for Glucosamine

Glucosamine plays a key role in the biochemistry of cartilage because it provides the building blocks for the synthesis of glycosaminoglycans, and thus of proteoglycans (see also Figure 2, § 3.0). This is the reason why early studies looked for the direct effects of Glucosamine on cartilage metabolism. Indeed, when exogenous Glucosamine is used at concentrations above 50 µM, it exerts both anabolic and anti-catabolic effects in cultured chondrocytes and intact cartilage tissue (Table 5) <sup>27,28</sup>.

**TABLE 5.**  
Pharmacological properties  
of Glucosamine at high concentrations

Pharmacological properties	Main findings
Anabolic effects	Glucosamine is preferentially incorporated by chondrocytes into glycosaminoglycan chains, where it promotes the synthesis of physiological proteoglycans <sup>27,28,29,30</sup>
Anti-catabolic effects	Glucosamine inhibits the expression and/or activity of catabolic enzymes such as phospholipase A2, matrix metalloproteinases, and aggrecanase <sup>31,32,33</sup>

These effects provide a basis for the use of Glucosamine as a dietary supplement to promote cartilage health. However, at the therapeutic dose of 1500 mg Glucosamine Sulfate, Glucosamine concentrations in biological fluids are probably insufficient to reach this aim <sup>34,35</sup> (see also Crystalline Glucosamine Sulfate—Pharmacokinetics, § 5.0).

The actual mechanism of action of Glucosamine in OA has recently been elucidated and is detailed below.

#### 4.2 The True Mechanism of Action of Crystalline Glucosamine Sulfate in OA

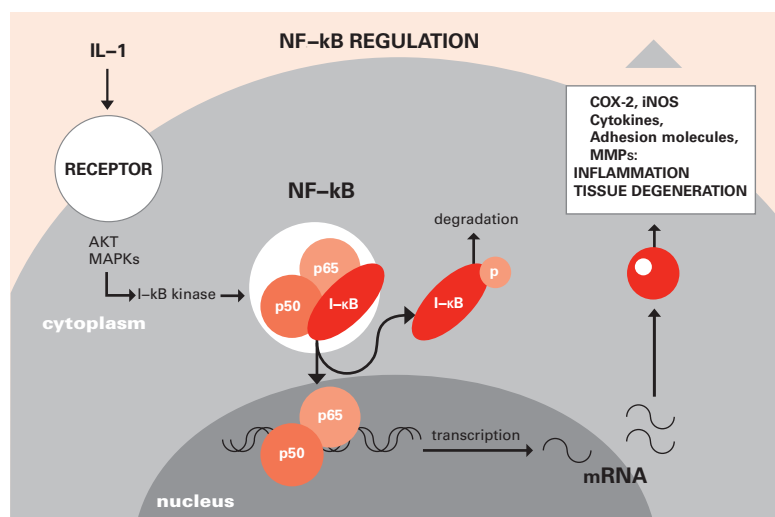
Recently, the anti-catabolic activity of Glucosamine has been associated with a reversal of the negative effects of interleukin (IL)–1 <sup>33,36,37</sup>, which results in decreased expression of key proinflammatory enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) <sup>38</sup>. Cytokine antagonism is believed to occur by virtue of an inhibitory effect on the IL–1 intracellular signaling pathway, in particular via inhibition of the transcription factor NF–kB (Figure 4) <sup>39,40</sup>.

**Researchers have demonstrated that Crystalline Glucosamine Sulfate (CGS)—the Rottapharm preparation of Glucosamine—inhibits IL–1-induced expression of different inflammatory and matrix degradation markers at Glucosamine concentrations of 10 µM or lower <sup>41</sup>. Such concentrations are similar to those found in the plasma and synovial fluid of osteoarthritis patients after repeated once daily administration of CGS at therapeutic doses (corresponding to 1500 mg Glucosamine Sulfate). Moreover, CGS also inhibits cytokine-induced expression of NF–kB subunits at even lower concentrations (Table 6). This mechanism might support both the symptom- and the structure-modifying effects of Glucosamine in OA, as long as the compound is formulated to reach the systemic circulation and the joint in sufficient concentrations.**

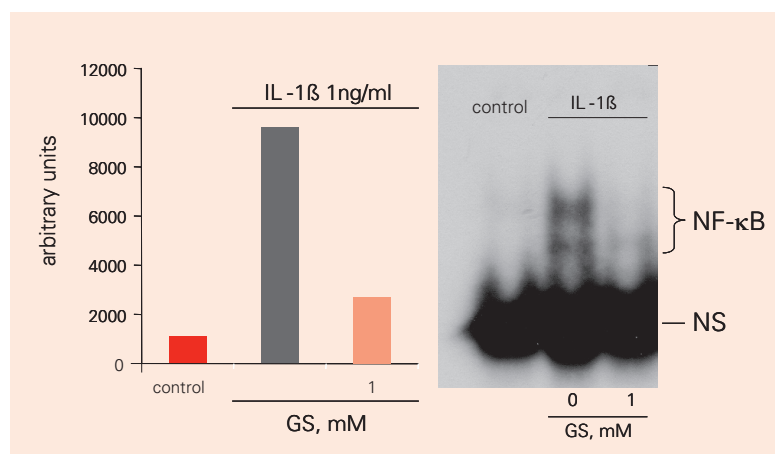
In addition to the primary role of Glucosamine itself, inorganic sulfates may contribute to the pharmacological effect of CGS in that they are essential for controlling the rate of glycosaminoglycan and proteoglycan synthesis. Because sulfate serum levels increase after the administration of Glucosamine Sulfate, special emphasis should be placed on the therapeutic use of sulfate salts of Glucosamine, compared to non-sulfate salts <sup>42</sup>.

**FIGURE 4.A**

Glucosamine inhibits IL-1-mediated events by inhibiting NF- $\kappa$ B activation

**FIGURE 4.B**

CGS reduces IL-1-induced NF- $\kappa$ B activation, as assessed by Electrophoretic Mobility Shift Assay (EMSA)

**TABLE 6.**

Crystalline Glucosamine Sulfate: IC<sub>50</sub> ( $\mu$ M  $\pm$  SE) on IL-1-induced gene expression of different inflammatory markers and NF- $\kappa$ B subunits.

Marker measured*	CGS IC <sub>50</sub> ( $\mu$ M)
COX-2	11.2 $\pm$ 1.2
iNOS	13.8 $\pm$ 5.6
IL-1 $\beta$	6.2 $\pm$ 3.0
MMP3	10.2 $\pm$ 2.3
ADAMTS5	2.8 $\pm$ 0.7
p50 (NF- $\kappa$ B1)	0.2 $\pm$ 0.1
p52 (NF- $\kappa$ B2)	0.3 $\pm$ 0.2
p65 (Rel A)	0.5 $\pm$ 0.9

\*Chondrocyte cultures were stimulated with IL-1 in the absence or presence of CGS

Moreover, Glucosamine Sulfate is a stronger inhibitor of gene expression than Glucosamine hydrochloride <sup>43</sup>, which may contribute to the different findings of clinical trials with different Glucosamine salts and formulations.

### 4.3 *In vivo* Pharmacology

The *in vivo* effects of Crystalline Glucosamine Sulfate on cartilage destruction were investigated in different experimental models.

#### *Rabbit osteoarthritis model* <sup>44</sup>

Knee OA was induced in rabbits by transection of the anterior cruciate ligament. CGS (120 mg/kg daily) was added to the drinking water of 6 animals immediately after surgery, and 6 animals were used as controls. All animals were sacrificed 8 weeks after surgery. Cartilage lesions were evaluated “blind” by the same observer on a 1-7 scale for macroscopic changes (1-softening, 2-localized superficial fibrillation, 3-large superficial fibrillation, 4-small erosion, 5-large erosion, 6-small bone exposure, and 7-large bone exposure). Overall assessment of chondropathy was performed on a 100 mm visual analogue scale (VAS), according to the method of Ayrat et al <sup>45</sup>. These methods of assessment were considered by arthroscopists to be reliable and sensitive. The results showed a significant reduction of cartilage destruction in animals treated with CGS. It was thus demonstrated experimentally that CGS has structure-modifying properties in osteoarthritis.

#### *Canine model of osteoarthritis* <sup>46</sup>

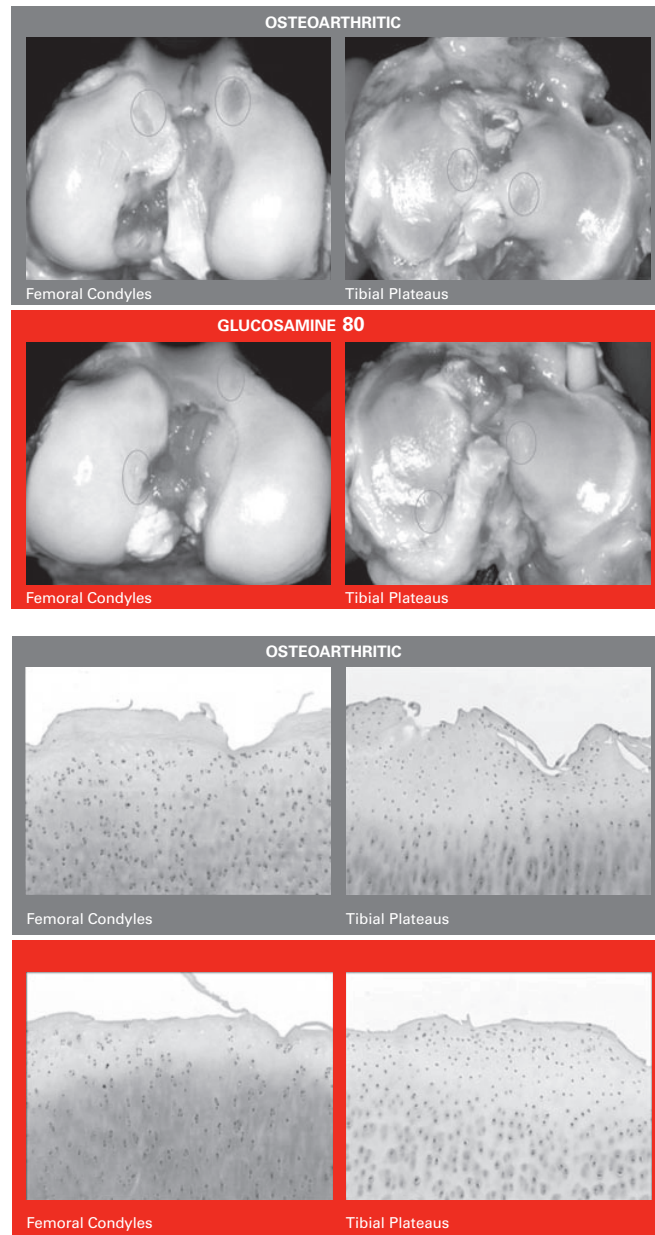
Osteoarthritic lesions were induced by transection of the anterior cruciate ligament (ACL), and the dogs were given either no treatment or CGS (80 mg/kg two times daily p.o.) for 8 weeks. CGS significantly decreased collagenase expression and activity in the cartilage and synovium. More importantly, CGS reduced the macroscopic and histological severity of cartilage lesions (Figure 5).

#### *STR/ort mouse model of osteoarthritis* <sup>47</sup>

STR/ort mice are considered a relevant model of human knee OA because they develop a naturally occurring OA of the tibiofemoral joint. Six-month-old male mice were used, and CGS or its vehicle was administered subcutaneously once daily at doses of 200 and 400 mg/kg body weight.

**FIGURE 5.**

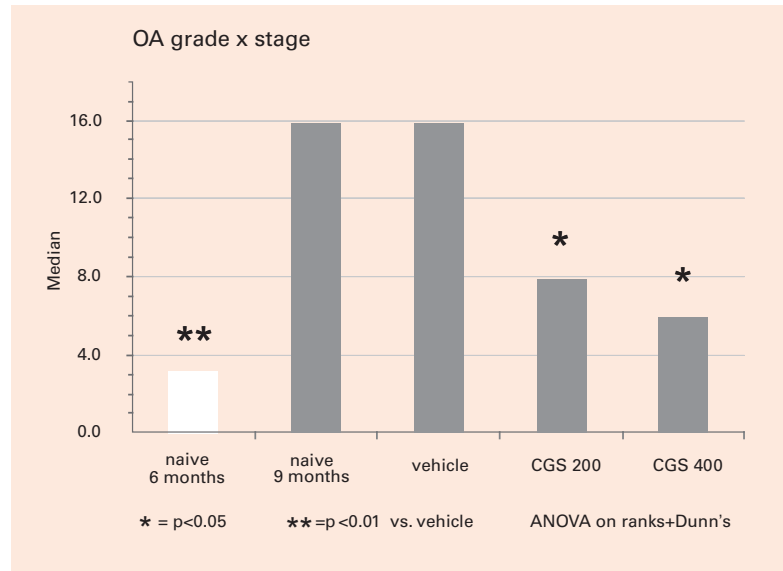
Macroscopic and histological severity of cartilage lesions after ACL in the dog: the effect of Crystalline Glucosamine Sulfate



These doses correspond to 950 and 1900 mg daily in humans, respectively, after allometric transformation. The animals were euthanized after 3 months of treatment, and the knee joints were collected, processed for histology, and scored in a blind fashion according to the OARSI (grade x stage) method.

**FIGURE 6.**

Effects of Crystalline Glucosamine Sulfate on OA progression in the STR/ort mouse



Both doses of CGS significantly reduced the severity of the disease—from a median of 16 to 8 and 6, respectively, at 200 and 400 mg/kg—in this relevant animal model of osteoarthritis (Figure 6).

## CHAPTER 5

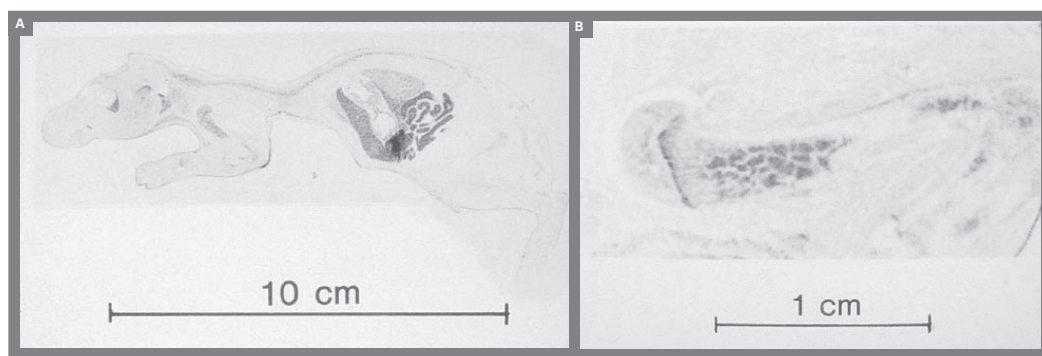
# Crystalline Glucosamine Sulfate Pharmacokinetics

Until recently, limited knowledge about the pharmacokinetics of Glucosamine (including oral bioavailability, peak plasma levels, and tissue distribution) hampered our full understanding of the relationships between the clinical effects of Glucosamine and its mechanism of action.

The main limitation was the lack of suitable methods for detecting unlabeled Glucosamine in biological fluids. Thus, preliminary evidence that Glucosamine actually reaches the joints came from autoradiographic studies in which rats were given the radioactive compound <sup>48</sup>. [<sup>14</sup>C] Glucosamine was diluted in unlabeled Crystalline Glucosamine Sulfate (CGS) and administered orally or intravenously at 20 µCi/kg body weight. [<sup>14</sup>C] Glucosamine entered most tissues rapidly. In particular, it was detected within the articular cartilage of various joints (Figure 7).

### FIGURE 7.

Autoradiograph of a rat 4 hours after oral administration of 20 µCi/kg of [<sup>14</sup>C] Glucosamine diluted in CGS. a) sagittal section of the body; b) detail of the distribution of radioactivity in bone and cartilage of the humerus



In past years, the impossibility of performing bioequivalence studies against the patented form of CGS favored the appearance on the market of

- undocumented Glucosamine salts,
- improperly stabilized Glucosamine Sulfate substances, and
- different dosage forms or regimens,

the clinical effects of which, when they have been studied, are clearly less favorable.

In recent years, specific and sensitive bioanalytical methods for the determination of Glucosamine in humans have become available <sup>49</sup>. Thus, the pharmacokinetic profile of Glucosamine after CGS administration has recently been described and is reported in the following pages.

CGS is now the only Glucosamine product the pharmacokinetics of which

- have been characterized in detail
- support the mechanism of action by which Glucosamine exerts symptom- and structure-modifying effects in OA.

## **5.1 The Pharmacokinetics of Crystalline Glucosamine Sulfate in Humans**

### ***5.1.1 Steady-state bioavailability and plasma pharmacokinetics of Glucosamine after increasing oral doses of CGS***

Twelve healthy volunteers were administered 3 consecutive once daily doses of CGS <sup>50</sup>. Each subject received 3 dose levels under fasting conditions in 3 study periods that were separated by a washout period of at least 3 days. The intermediate dose level of this study was selected based on the therapeutic dose of 1500 mg/day (with reference to GS). The other two dose levels corresponded to half (750 mg) and twice (3000 mg) the therapeutic dose.

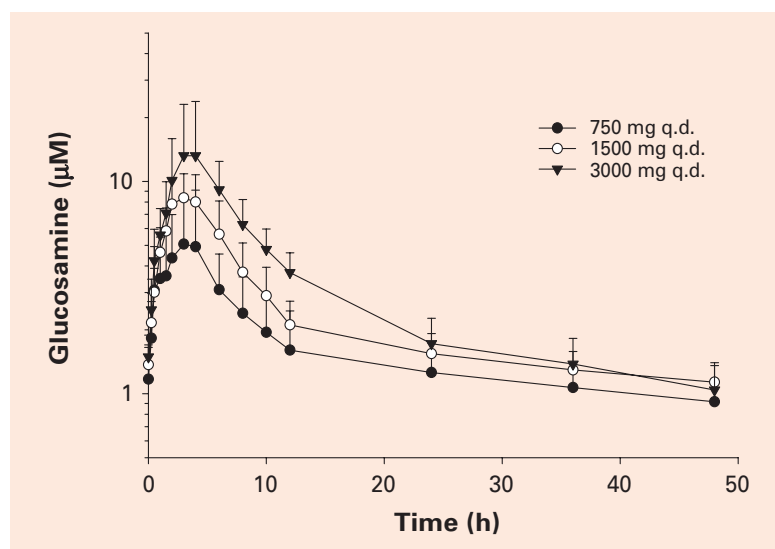
Endogenous Glucosamine was detected in all plasma samples collected before drug administration. The basal concentrations ranged from 10.4 to 204 ng/mL (corresponding to 0.06 and 1.1  $\mu$ M, respectively). Regardless of this high degree of inter-subject variability, mean values did not differ significantly either between males and females or across the 3 study periods.



Glucosamine was rapidly absorbed and available to the systemic circulation. Steady state was reached with the third administration. Peak concentrations were achieved within 3-4 hours (median  $T_{max}$ ) and were in the 10  $\mu\text{M}$  range with the standard therapeutic once daily dosage of 1500 mg (Figure 8). The median peak steady-state plasma concentration ( $C_{ss, max}$ ) at this dose was actually 9.92  $\mu\text{M}$  (1777.6 ng/mL). Thereafter, plasma concentrations of Glucosamine decreased slowly and were consistently above baseline levels 48 hours after dosing in all subjects and at all doses. The elimination half-life of Glucosamine was estimated to be about 15 hours, which supports once daily administration.

**FIGURE 8.**

Mean ( $\pm$ SD) Glucosamine plasma concentration vs. time profiles at steady state after repeated once daily doses of CGS corresponding to 750, 1500, and 3000 mg GS (n=12 for each dose level)



#### CONCLUSION

**After therapeutic doses of CGS, plasma Glucosamine levels are in the range (~10  $\mu\text{M}$ ) at which Glucosamine is expected to be pharmacologically active (i.e., to inhibit IL-1-induced gene expression).**

### 5.1.2 Synovial Glucosamine concentrations after CGS at the therapeutic dose

A study was undertaken to test whether Glucosamine reaches the joints after 14-day oral administration of CGS at the therapeutic dose of 1500 mg (as GS) once daily<sup>51</sup>. Twelve patients (6 males and 6 females) with knee OA received 14 consecutive once daily oral doses of CGS. Plasma and synovial fluid samples were collected simultaneously from the same patient, at baseline and at steady-state.

The median endogenous Glucosamine concentrations in plasma and synovial fluid were 52.0 ng/mL (0.29 µM) and 36.5 ng/mL (0.21 µM), respectively ( $p=0.001$ ), and varied greatly among patients (41-121 ng/mL and <10-67 ng/mL, respectively). Three hours after the last dose, median Glucosamine concentrations increased 20.5- and 21.5-fold, in plasma and synovial fluid respectively. This suggests that after CGS administration, Glucosamine has a similar distribution between the two compartments. Post-treatment Glucosamine levels ranged from 600 to 4061 ng/mL (3.35-22.7 µM) in plasma and from 577 to 3248 ng/mL (3.22-18.1 µM) in synovial fluid (Table 7). Thus, plasma and synovial Glucosamine concentrations were highly correlated (Figure 9), and were in the 10 µM range.

**TABLE 7.**

Glucosamine levels in plasma and synovial fluid, 3 hours after the last drug administration. Fold increases over baseline values are shown in brackets

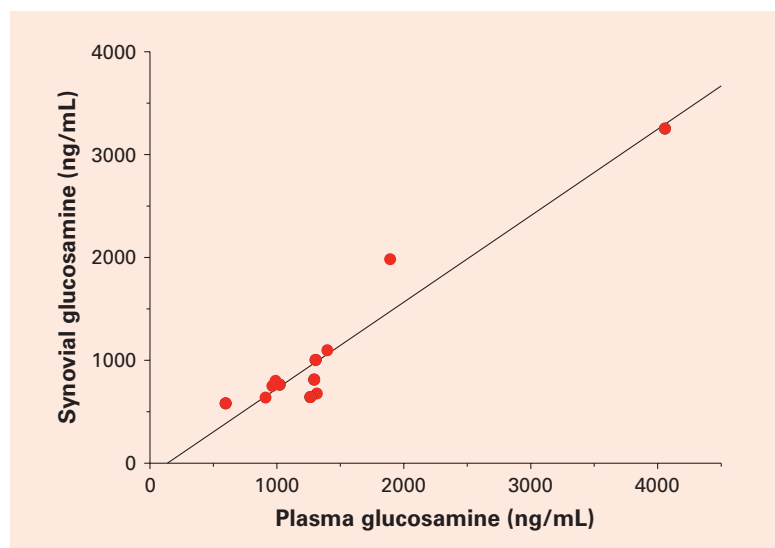
	Plasma		Synovial fluid	
	ng/mL	µM	ng/mL	µM
Median	1282 (20.5)	7.17	777 (21.5)	4.34
Range	600-4061 (8-90)	3.35-22.7	577-3248 (10->197.8)	3.22-18.1

### CONCLUSIONS

**Glucosamine synovial levels after therapeutic doses of CGS are in the range (~10 µM) at which Glucosamine is expected to inhibit the expression of inflammatory and matrix degradation markers.**

**FIGURE 9.**

Correlation between plasma and synovial fluid Glucosamine concentrations. The correlation is described by the equation  $y=0.84x - 115.6$  ( $r=0.96$ )



### 5.1.3 Crystalline Glucosamine Sulfate vs. Glucosamine hydrochloride (alone or in combination with chondroitin sulfate)

As reported above, the pharmacokinetics of CGS show peak plasma Glucosamine levels in the 10  $\mu$ M range. *In vitro* studies have demonstrated that these levels are effective in counteracting IL-1-induced gene expression, an effect that is currently regarded as the mechanism of action of Glucosamine in OA.

Conversely, studies of Glucosamine pharmacokinetics after administration of the Glucosamine hydrochloride (G-HCl) formulation used in the NIH-sponsored GAIT trial suggested that the peak levels might be lower<sup>52,53,54</sup>. Based on the pharmacokinetic data shown in Table 8, the negative results with Glucosamine hydrochloride in OA patients may not be so surprising (see the Clinical Efficacy section for a discussion of this aspect; § 6.5)<sup>54</sup>.

On the other hand, it is evident that pharmacokinetic data cannot be directly compared unless generated within the same study. It was therefore necessary to investigate, in a direct comparative study, the relative bioavailability of Glucosamine after repeated oral administration of the Glucosamine salts, formulations, and dose regimens used in the GUIDE (CGS) and GAIT (G-HCl) trials. Thus, twelve healthy volunteers (5 males and 7 females) were randomized in a crossover design to receive CGS powder for oral solution 1500 mg once daily or Glucosamine hydrochloride capsules

	CGS 1500 mg u.i.d. Steady State <sup>50</sup>	G-HCl 500 mg t.i.d. Steady State <sup>53</sup>	G-HCl 1500 mg u.i.d. Single Dose <sup>52</sup>
<b>C<sub>max</sub> (mean)</b>			
• ng/mL	1602±425	211±94	545±155
• μM	8.9±2.4	1.2±0.5	3.0±0.9
<b>T<sub>1/2</sub> (hours)</b>	15	3.9	3.3
<b>Reference clinical trial and outcome for each salt, formulation, and regimen</b>			
	CGS 1500 mg once daily GUIDE trial (positive results in OA)	G-HCl 500 mg t.i.d. GAIT trial (negative results in OA)	—
u.i.d., once daily; t.i.d., three times daily			

**TABLE 8.**

Pharmacokinetic parameters after CGS 1500 mg (u.i.d.), Glucosamine hydrochloride 1500 mg (u.i.d.), or Glucosamine hydrochloride 500 mg (t.i.d.)

500 mg t.i.d. (either alone or in combination with chondroitin sulfate 400 mg t.i.d.) <sup>55</sup> for 3 days. Glucosamine was determined at steady state, in plasma collected up to 48 hours after the last dose, by a validated Liquid Chromatography/Mass Spectrometry (LC-MS/MS) method.

Glucosamine was bioavailable following administration of the three different treatments. After CGS 1500 mg once daily, peak concentrations ( $C_{ss, max}$ ) and extent of exposure ( $AUC_{ss}$ ) averaged  $9.1 \pm 6.3 \mu M$  and  $76.5 \pm 23.0 \mu M \cdot h$  respectively. Significantly lower plasma concentrations were found after the administration of 500 mg Glucosamine hydrochloride alone ( $C_{ss, max}$  and  $AUC_{ss}$  averaged  $4.5 \pm 1.8 \mu M$  and  $21.4 \pm 7.6 \mu M \cdot h$ , respectively), or in combination with chondroitin sulfate ( $C_{ss, max}$  and  $AUC_{ss}$  averaged  $3.3 \pm 1.0 \mu M$  and  $13.7 \pm 5.4 \mu M \cdot h$ , respectively). Detailed results are presented in Table 9 and Figure 10.

## CONCLUSION

**Glucosamine hydrochloride 500 mg three times daily might produce an extent of exposure similar to that of CGS 1500 mg once daily, but at significantly lower (less than half) peak plasma concentrations of Glucosamine. Such lower concentrations might not reach the phar-**

	CGS	G-HCl	G-HCl + CS
$C_{ss, \max}$ (ng/mL)	1623.6±1131.6†	798.4±317.3	588.9±181.5
$C_{ss, \max}$ (μM)	9.1±6.3†	4.5±1.8	3.3±1.0
$AUC_{ss}$ (ng·h/mL)	13712±4112†	3839±1370	2463±962
$T_{\max}$ (h)*	3(3-4)	3(1-4)	3(1-6)

CGS, Crystalline Glucosamine Sulfate; G-HCl, Glucosamine hydrochloride; CS, chondroitin sulfate  
 \*median and range. †p<0.05 vs. G-HCl and vs. G-HCl +CS.

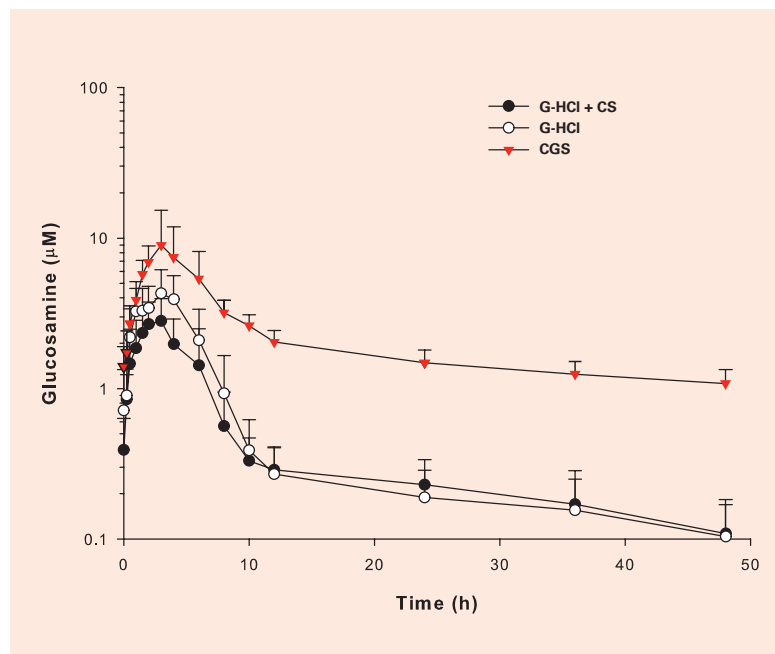
**TABLE 9.**

Glucosamine pharmacokinetic parameters (mean ±SD) after the administration of the three drugs in the study

**macologically effective threshold. This finding could explain the lack of efficacy of Glucosamine hydrochloride in OA. The combination of Glucosamine hydrochloride and chondroitin sulfate further reduces the bioavailability of Glucosamine.**

**FIGURE 10.**

Mean (±SD) Glucosamine plasma concentration (μM) vs. time profile after repeated doses of CGS or G-HCl alone or in combination with CS (n=12 for each study medication)





## CHAPTER 6

# Crystalline Glucosamine Sulfate Clinical Efficacy in OA

Crystalline Glucosamine Sulfate (CGS) is the original Glucosamine product which was made available for human use and specifically developed by Rottapharm as a prescription drug for the treatment of osteoarthritis. CGS is the only form of Glucosamine used in successful clinical trials conducted for scientific and regulatory purposes. Thus, CGS should not be confused with other forms of “Glucosamine” widely employed as dietary supplements or generics in different salts, formulations, dosages, or combinations. The effects of most of these products have not yet been assessed in clinical studies.

Conversely, CGS has been evaluated in over 25 controlled and non-controlled studies involving more than 7000 patients with OA. This comprehensive clinical program includes short- and medium-term studies on symptoms and long-term studies on structural changes and symptoms. The core evidence of efficacy is represented by the results of three pivotal trials<sup>56,57,58</sup>, which support the favorable effects of Glucosamine on the symptoms and progression of OA. The once daily CGS formulation used in pivotal studies is virtually identical to the sachet formulation that is marketed worldwide.

For practical reasons, studies of CGS have been classified based on whether they were designed to assess the efficacy of GCS as a symptom-modifying or a structure-modifying drug in OA. High-quality trials are summarized in the following pages.

### The efficacy of CGS in OA: a summary of the evidence from pivotal clinical trials

- The efficacy of CGS on OA symptoms in 6-month and 3-year trials is comparable to that of NSAIDs for much shorter treatments
- Two 3-year studies have shown, for the first time with any pharmacological intervention for OA, a significant delay in the progression of joint structure changes. These results indicate that CGS has structure-modifying properties and may therefore be a disease-modifying agent
- The long-term follow-up of patients enrolled in clinical studies indicates that CGS reduces disability and surgical joint replacement

## 6.1 Studies Designed to Assess the Efficacy of CGS as a Symptom-Modifying Drug in OA

### 6.1.1 Supportive clinical trials vs. placebo

The early clinical studies of the original CGS consisted of four randomized, controlled trials, mostly short-term (weeks or months) <sup>59,60,61,62</sup>. Although conducted when the knowledge about clinical trial methodology for OA was still poor, these studies provided good evidence of efficacy on OA symptoms at different joint localizations. Moreover, they led to marketing approval of CGS and support the daily dose that has been used in more recent trials, which are detailed in this section.

### *Crystalline Glucosamine Sulfate in osteoarthritis of the knee* <sup>63</sup>

#### *Objective*

- To evaluate the efficacy and safety of CGS on the symptoms of knee OA.

#### *Study design*

- Randomized, placebo-controlled, double-blind, parallel-group study. Treatment duration was 4 weeks, with weekly assessments of clinical status.

#### *The treatment arms were:*

- CGS 1500 mg/day, oral (N=126).
- Placebo (N=126).

#### *Inclusion criteria*

- Osteoarthritis of the knee (Lequesne criteria). Lequesne algofunction-



al index of at least 4 points and symptoms for at least 6 months before enrollment.

*Total no. of patients and study endpoints*

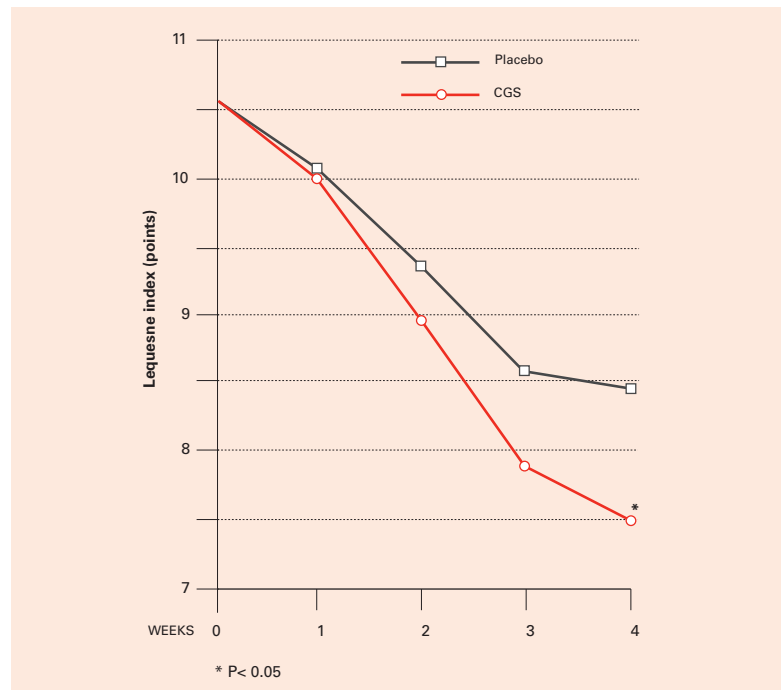
- Two hundred fifty-two patients, mean age 55 years, 60% female.
- The main evaluation criterion was the Lequesne algofunctional index<sup>64</sup>, in conjunction with the investigator's overall judgment of effectiveness. Responders were defined as patients with a reduction of at least 3 points in the Lequesne index and a positive overall assessment by the investigator.

*Results*

- After 4 weeks, GGS was more effective than placebo in improving the Lequesne index score (Figure 11), with a higher responder rate: 52% vs. 37% based on an intent-to-treat analysis ( $p=0.016$ ).
- The beneficial effects of CGS occurred as early as 2 weeks after the treatment began.

**FIGURE 11.**

Changes in the Lequesne index. Weeks 0–4



**CONCLUSIONS**

**CGS is effective in improving OA symptoms in the short-term.**

### *Efficacy of Crystalline Glucosamine Sulfate in osteoarthritis of the spine<sup>65</sup>*

#### *Objective*

- To evaluate the efficacy and safety profile of oral CGS in controlling the symptoms of osteoarthritis of the spine.

#### *Study design*

- Placebo-controlled, double-blind, parallel-group study. Treatment duration was 6 weeks, followed by a 4-week treatment-free follow-up period.

#### *The treatment arms were:*

- CGS 1500 mg once daily (N=43).
- Placebo (N=49).

#### *Inclusion criteria*

- Patients diagnosed as having cervical and/or lumbar OA on the basis of chronic pain (>6 months) and stiffness/functional limitation, plus radiological signs of disease activity.

#### *Total no. of patients and study endpoints*

- One hundred sixty patients, mean age 64 years, 82% female.
- The response rate was based on the investigator's overall judgment of effectiveness .

#### *Results*

- More than 51% of patients randomized to CGS were reported to have either "improved" or "definitely improved" symptoms, compared with 28.6% in the placebo group ( $p=0.034$ ).
- Pain at rest, pain at movement, tenderness, night pain, and rotational movement (degrees) improved more with CGS than with placebo. The positive effects were maintained for 4 weeks after the discontinuation of CGS. Figure 12 shows the change in visual analogue scale (VAS) scores over time (lumbar pain).

### **CONCLUSIONS**

**CGS is effective in the treatment of osteoarthritis of the spine. The beneficial effects are maintained for 4 weeks after the discontinuation of GCS.**

**FIGURE 12.**

VAS scores for lumbar pain at rest. Weeks 0–10



### 6.1.2 Supportive clinical trials vs. NSAIDs

#### Crystalline Glucosamine Sulfate vs. ibuprofen <sup>66</sup>

##### Objective

- To compare the effects of CGS and ibuprofen on the symptoms of knee OA.

##### Study design

- Randomized, reference-controlled, double-blind, multicenter, prospective, parallel-group trial. Treatment duration was 4 weeks.

##### The treatment arms were:

- CGS 1500 mg/day, oral (N=100).
- Ibuprofen 1200 mg/day, oral (N=99).

##### Inclusion criteria

- Osteoarthritis of the knee (Lequesne criteria), with symptoms for at least 3 months before enrollment and a Lequesne index of at least 7 points.

##### Total no. of patients and study endpoints

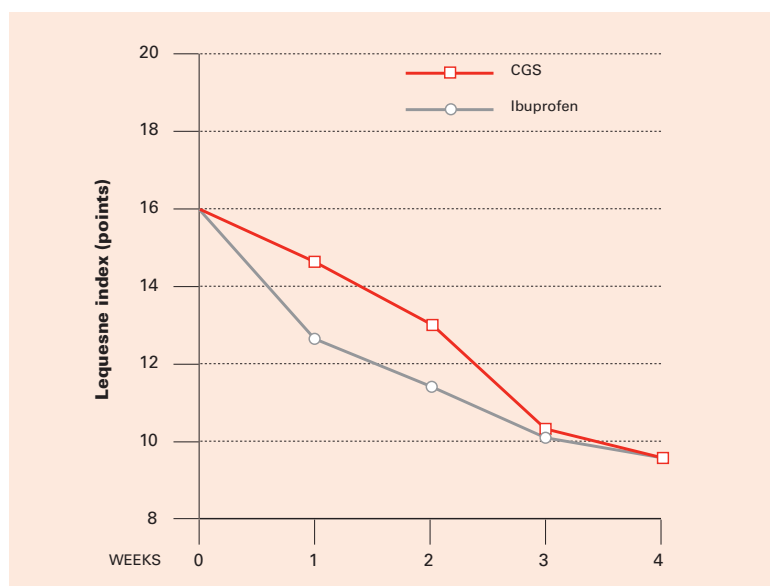
- One hundred ninety-nine patients, mean age 54 years, 48% female.

- The main evaluation criterion was based on the Lequesne index, together with a positive overall assessment by the investigator.

#### Results

- After 4 weeks of treatment, both CGS and ibuprofen decreased the Lequesne index by about 40%. There were no significant differences between the two groups (Figure 13).
- The responder rate was 48% for CGS and 52% for ibuprofen ( $p=0.67$ ).
- Although ibuprofen had a faster onset of action than CGS, the beneficial effects of CGS were observed within 2 weeks of treatment and thereafter were similar to those of the NSAID.

**FIGURE 13.**  
Changes in the Lequesne index. Weeks 0–4.



These results were confirmed in a similar randomized, double-blind study of CGS vs. ibuprofen in an ethnically different population (178 Chinese patients) <sup>67</sup>.

#### CONCLUSIONS

**CGS is as effective as the NSAID ibuprofen in relieving the symptoms of osteoarthritis. The onset of action of CGS is observed within 2 weeks. The similar efficacy between the two drugs should be considered in the broader context of a chronic treatment, because CGS is associated with significantly fewer adverse events than ibuprofen (see Safety section, § 7.1).**

### *Crystalline Glucosamine Sulfate vs. piroxicam*<sup>68</sup>

#### *Objective*

- To compare the effects of CGS, a placebo, piroxicam, and a combination of CGS and piroxicam on the symptoms of knee OA.
- To study the “time-effect relationship” of CGS (onset of action and duration of effect after treatment withdrawal).

#### *Study design*

- Randomized, placebo and reference-controlled, double-blind, double-dummy, multicenter, prospective, parallel-group trial. Treatment duration was 12 weeks, followed by an 8-week treatment-free follow-up period.

#### *The treatment arms were:*

- CGS 1500 mg, oral, once daily (N=79).
- Piroxicam 20 mg, oral, once daily (N=86).
- CGS 1500 mg + piroxicam 20 mg once daily (N=77).
- Double placebo (N=77).

#### *Inclusion criteria*

- Osteoarthritis of the knee, according to the criteria formulated by Lequesne and those of the American College of Rheumatology. Patients had to have a minimum score of 4 points on the Lequesne algofunctional index and global knee pain  $\geq 40$  mm on a 100 mm VAS.

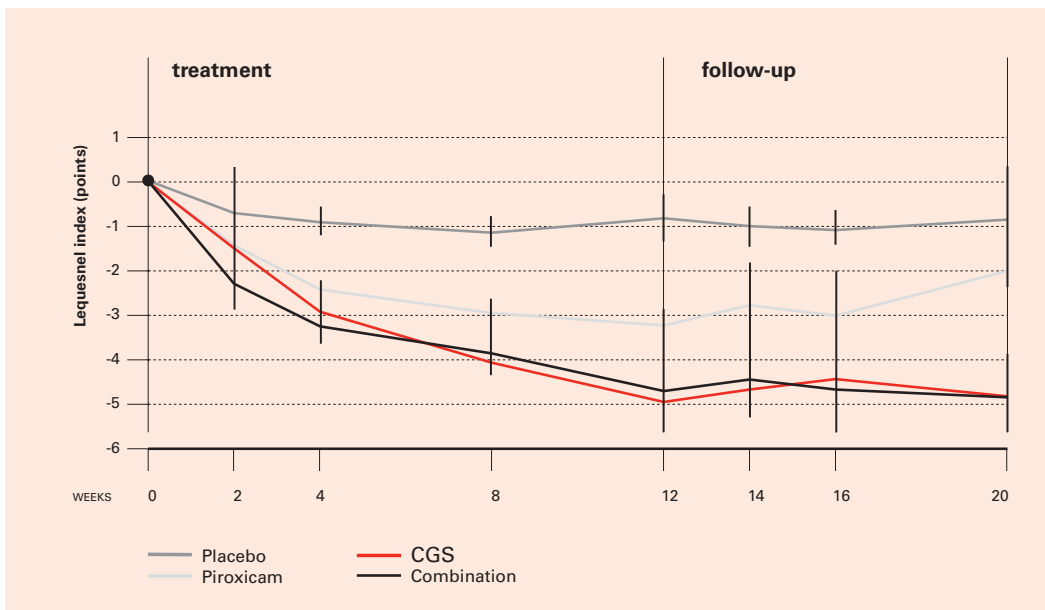
#### *Total no. of patients and study endpoints*

- Three hundred nineteen patients, mean age 66 years, 74% female.
- The main outcome measure was the Lequesne algofunctional index of severity for knee osteoarthritis.

#### *Results*

- CGS 1500 mg once daily was effective in improving the symptoms of osteoarthritis. At the end of the 3-month treatment period, the Lequesne algofunctional index decreased on average by nearly 5 points (Figure 14).
- With CGS, the onset of symptom relief was already evident after 2 weeks, and was similar to that observed with piroxicam alone.
- After 4 weeks, the improvement with CGS was greater than that with piroxicam. At the end of the 3-month treatment period, piroxicam was less effective than CGS: the Lequesne algofunctional index decreased by 27% in the piroxicam group and by 47% in the CGS group ( $p < 0.05$ ).

- Both CGS and piroxicam were more effective than the placebo ( $p < 0.001$ ) in reducing the signs and symptoms of osteoarthritis.
- There were no significant differences between the CGS group and the combination (CGS + piroxicam) group in terms of efficacy. Combined therapy tended to have a faster onset of action during the first 2 weeks.
- The effect of CGS (or of the combined therapy) was maintained up to 8 weeks after drug withdrawal ("carryover effect";  $p < 0.01$  vs. placebo).
- This long-lasting effect was not observed in the piroxicam group.



**FIGURE 14.**

Mean change from baseline in the Lequesne index score (in points, with 95% CI) at each appointment during the treatment period (left) or the follow-up (right)

#### CONCLUSIONS

**CGS is more effective than piroxicam in controlling the symptoms of osteoarthritis over a 3-month treatment period. Combined therapy (CGS plus an NSAID) might produce a faster onset of symptom relief during the first 2 weeks of treatment. The beneficial effects of CGS are maintained for at least 8 weeks after drug withdrawal, while this is not the case with piroxicam.**

### **6.1.3 The pivotal study of CGS as a symptom-modifying drug in OA: results from the Glucosamine Unum In Die Efficacy (GUIDE) trial**

#### *Objective*

- To assess the efficacy and safety of CGS on the symptoms of knee OA during a 6-month course of treatment<sup>58</sup>. Acetaminophen (paracetamol), the currently preferred medication for symptomatic treatment of OA, was used as a side comparator.

#### *Study design*

- Multicenter, prospective, randomized, double-blind (double-dummy), placebo- and reference-controlled trial.

#### *The treatment arms were:*

- CGS powder for oral solution 1884 mg once daily in single-dose sachets (equivalent to 1500 mg of Glucosamine Sulfate; N=106).
- Acetaminophen 3000 mg/day (one 1000 mg tablet three times daily; N=108).
- Placebo (N=104).

#### *Inclusion criteria*

- Primary osteoarthritis of one or both knees, according to the clinical and radiographic criteria of the American College of Rheumatology.

#### *Total no. of patients and study endpoints*

- Three hundred eighteen patients in the ITT population, mean age between 60 and 65 years, 88% female.
- The primary efficacy outcome was the change in the Lequesne algofunctional index of severity for OA of the knee<sup>64-B</sup>. The secondary efficacy endpoints were the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index<sup>69-C</sup> and the Osteoarthritis Research Society International (OARS) responder criteria<sup>70-D</sup>.

<sup>B</sup> A disease-specific, aggregated multidimensional index consisting of 5 questions addressing knee pain, 4 questions on knee function in daily living, and a scale of maximum distance walked. The worst possible total index score is 24, but the disease is considered extremely severe if the score is >13<sup>64</sup>.

<sup>C</sup> The 0–4-point Likert scale (LK 3.0) - WOMAC version - was used, addressing severity of knee pain (5 questions), limitation of physical function (17 questions), and stiffness (2 questions) in the 48 hours before assessment. The worst possible scores on the WOMAC subscales are therefore 20, 68, and 8 in the 3 domains, respectively, and can be used to normalize the Likert scores to a 0–100 scale, i.e., similar to a 100-mm visual analog scale (VAS)<sup>69</sup>.

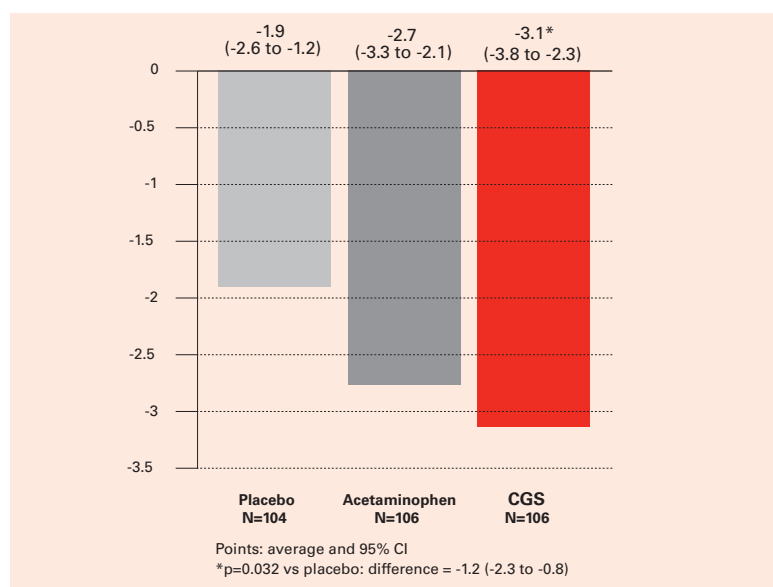
<sup>D</sup> The OARS-A responder criteria for oral OA-specific drugs consist of a dichotomous outcome measure that defines as responders those patients with either a high degree of improvement in pain (at least 55% relative change on the WOMAC pain subscale, with an absolute change of at least 30 on a 0–100 standardized scale) or moderate improvement in 2 of the 3 domains

### Results

- The treatment groups were comparable in terms of demographic and baseline disease characteristics.
- CGS was significantly more effective than the placebo on the 6-month primary efficacy outcome (Lequesne index, ITT analysis), whereas acetaminophen failed to reach a significant effect (Figure 15 and Table 10).
- The clinical relevance of the effect size of CGS vs. placebo (0.32; 0.05-0.59) on the primary outcome was confirmed by the higher proportion of responders according to the OARSI-A criteria (39.6% vs. 21.2% in the placebo group;  $p=0.004$ ). Acetaminophen also had more responders than the placebo (33.3%,  $p=0.047$ ).
- CGS was significantly superior to the placebo in reducing the WOM-AC total index, whereas no significant differences vs. placebo were found in the acetaminophen group (Table 10).
- More patients on the placebo (91%) used ibuprofen as a rescue medication ( $p=0.027$  and  $0.045$  vs. CGS [78%] and acetaminophen [79%], respectively).

**FIGURE 15.**

Intent-to-treat change in symptom scores (points: mean and 95% CI) after 6 months in GUIDE: primary outcome (Lequesne index)



of pain, function (on the WOMAC physical function subscale), and patient global assessment (35%, 15%, and 15% relative changes, with 10, 20, and 15 standardized units of absolute change, respectively). The OARSI-B responder criteria requires a high degree of improvement in pain or function, or moderate improvement in 2 of the 3 domains listed above <sup>70</sup>.



	Placebo (n=104)		Acetaminophen (n=108)		Crystalline Glucosamine Sulfate (n=106)	
	Baseline	6 months	Baseline	6 months	Baseline	6 months
Lequesne (points)*	10.8 (2.6)	-1.9 (-2.6 to -1.2)	11.1 (2.7)	-2.7 (-3.3 to -2.1)	11.0 (3.1)	-3.1* (-3.8 to -2.3)
WOMAC (points)*	37.9 (14.3)	-8.2 (-11.3 to -5.1)	40.4 (14.8)	-12.3 (-14.9 to -9.7)	38.3 (15.2)	-12.9† (-15.6 to -10.1)
OARSI-A responders (%)	-	21.2	-	33.3‡	-	39.6§

\*Mean absolute (SD) at baseline and change (95%CI) at 6 months.  
p vs. placebo: \* 0.032 [difference= -1.2 (-2.3 to -0.8)]; † 0.039 [difference= -4.7 (-9.1 to -0.2)]; ‡ 0.047; § 0.004

**TABLE 10.**

Changes in the Lequesne and WOMAC indexes (ITT), and % of patients meeting the secondary efficacy outcome measure (responders according to the OARSI-A criteria)

**CONCLUSION**

**CGS 1500 mg once daily should be the preferred symptomatic medication for medium and long-term treatments in patients with knee OA. In fact, CGS is at least as effective as acetaminophen—the preferred treatment in OA practice guidelines—in improving OA symptoms (as measured by the Lequesne and WOMAC indexes). Furthermore, the proportion of responders to CGS is higher than the proportion of responders to acetaminophen and placebo, as assessed by the OARSI-A responder criteria.**

## 6.2 Pivotal Studies Designed to Assess the Efficacy of CGS as a Structure-Modifying Drug in OA

The studies summarized in the previous section demonstrated that CGS improves the symptoms of osteoarthritis. CGS acts in a way that is different from that of unspecific symptomatic medications (e.g., NSAIDs), including a more progressive action and a distinct long-lasting effect. The latter may underlie changes in the evolution of the disease. However, scientific organizations and health regulatory authorities agree that disease modification should be achieved by stopping or delaying joint pathological changes by a so-called structure-modifying effect<sup>12,13,11,71</sup>. As it is impossible to perform a pathology assessment, it is acknowledged that joint space narrowing (JSN), measured by radiographic methods represents a good indicator of structural changes to the joint.

Two 3-year pivotal studies have shown, for the first time with any pharmacological intervention for OA, that CGS significantly delays the progression of joint structure changes, as assessed by radiographic measurements of joint space width (JSW) and joint space narrowing (JSN). These results indicate that CGS has structure-modifying properties and may be therefore a disease-modifying agent. A summary of these two pivotal studies is presented in the following subsections.

### **6.2.1 Long-term effects of CGS on OA progression: a randomized, placebo-controlled clinical trial**

#### *Objective*

- To assess the effects of CGS on the long-term progression of joint structure changes and symptoms in patients with osteoarthritis <sup>56</sup>.

#### *Study design*

- Randomized, placebo-controlled, double-blind, parallel group study. Treatment duration was 3 years.

#### *The treatment arms were:*

- CGS powder for oral solution 1884 mg once daily (equivalent to 1500 mg of Glucosamine Sulfate; N=106).
- Placebo (N=106).

#### *Inclusion criteria*

- Osteoarthritis of the knee, according to the American College of Rheumatology (ACR) criteria.

#### *Total no. of patients and study endpoints*

- Two hundred twelve patients (106 in each group), mean age 66 years, 76% female.
- Weight-bearing, anteroposterior radiographs of each knee in full extension were taken at enrolment and after 1 and 3 years. The primary structural endpoint was joint space narrowing (JSN) evaluated by digital image analysis of mean joint space width (JSW) in the medial compartment of the tibiofemoral joint, as well as by visual inspection (with the aid of a magnifying lens) at the narrowest point.
- The primary endpoint for symptom relief was the WOMAC index.

#### *Results*

- Patients had similar mild to moderate radiographic grading and JSW at enrolment, with mild to moderate symptoms.

- CGS was effective in preventing structure changes and in controlling symptoms.
- Placebo-treated patients suffered a mean JSN of about -0.1 mm/year, which is in line with data reported in the literature. No narrowing occurred on average in the CGS group. The final differences between groups were significant (Table 11).
- Furthermore, 30% of patients randomized to placebo had a severe mean JSN > 0.5 mm, which may predict disability in the future, compared with only 15% of patients on CGS ( $p = 0.013$ ).

	Placebo	CGS	Difference	p
JSW at enrollment, mm (mean $\pm$ SD)	3.95 $\pm$ 1.24	3.82 $\pm$ 1.32	-	-
<b><i>Intent-to-treat analysis</i></b>	(n=106)	(n=106)		
3-year JSN, mm (mean and 95% CI)	-0.40 (-0.56 to -0.24)	-0.07 (-0.22 to 0.07)	0.33 (0.12 to 0.54)	0.003
<b><i>Patients assessed for 3 years</i></b>	(n=71)	(n=68)		
3-year JSN, mm (mean and 95% CI)	-0.40 (-0.64 to -0.17)	0.11 (-0.10 to 0.33)	0.51 (0.20 to 0.83)	0.002

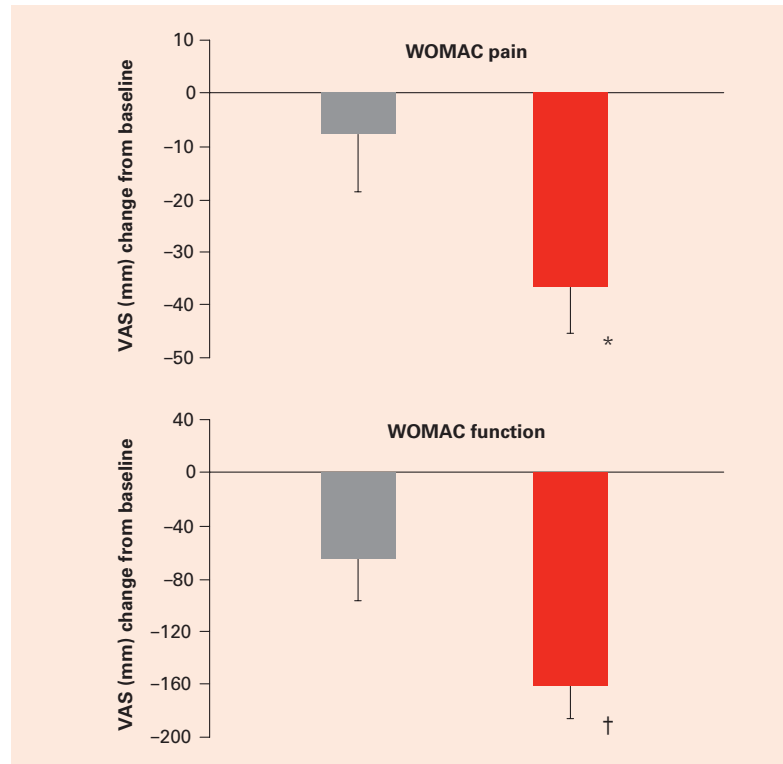
**TABLE 11.**

The effect of CGS on joint space (0–3 years)

- After 3 years, there was an improvement in the primary symptom outcome measure (total WOMAC index) in the CGS group (-11.7%, ITT; -24.3%, completers). Conversely, the symptoms of patients treated with the placebo worsened (9.8% in both ITT and completers). There were significant improvements in WOMAC pain and function subscales with CGS vs. placebo (Figure 16).

**FIGURE 16.**

Intent-to-treat mean (SE) change in WOMAC pain and function after 3 years. Red bars=CGS; gray bars=placebo. \* $p=0.047$ ; † $p=0.020$ . VAS=visual analogue scale



### 6.2.2 The use of CGS and delay of the progression of OA: a 3-year, randomized, placebo-controlled, double-blind study

#### Objective

- To confirm, in an independent trial, the effects of CGS on the long-term progression of joint structure changes and symptoms in patients with osteoarthritis <sup>57</sup>

#### Study design

- Randomized, placebo-controlled, double-blind, parallel group study. Treatment duration was 3 years.

#### The treatment arms were:

- CGS powder for oral solution 1884 mg once daily (equivalent to 1500 mg of Glucosamine Sulfate; N=101).
- Placebo (N=101).

#### Inclusion criteria

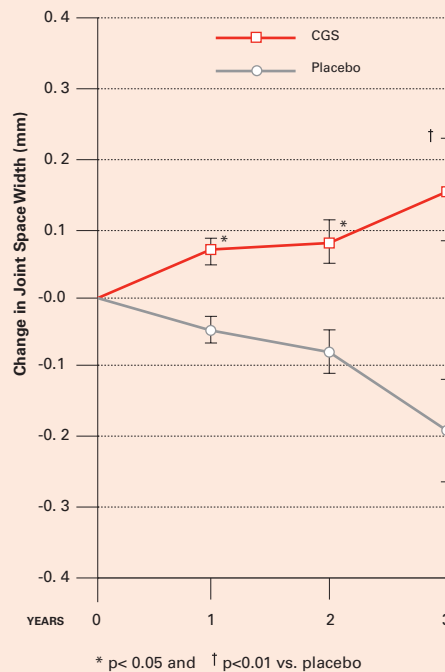
- Osteoarthritis of the knee, according to the ACR criteria.

*Total no. of patients and study endpoints*

- Two hundred two patients, mean age 62 years, 78% female.
- Weight-bearing, anteroposterior radiographs of each knee were taken at enrollment and after 1, 2, and 3 years, with the knees in full extension.
- The primary structural endpoint was joint space narrowing (JSN) at the narrowest medial compartment of the tibiofemoral joint.
- Symptoms were evaluated primarily by the Lequesne algofunctional severity index.

*Results*

- Patients in the two groups had similar baseline demographic and disease characteristics and represented a sample of the general population with osteoarthritis.
- CGS was superior to the placebo in preventing structure changes and in controlling symptoms.
- After 3 years, placebo-treated patients had an average JSN of about  $-0.2$  mm, whereas no narrowing occurred in the CGS-treated group (Figure 17). The difference between groups was highly significant ( $p=0.001$ ).

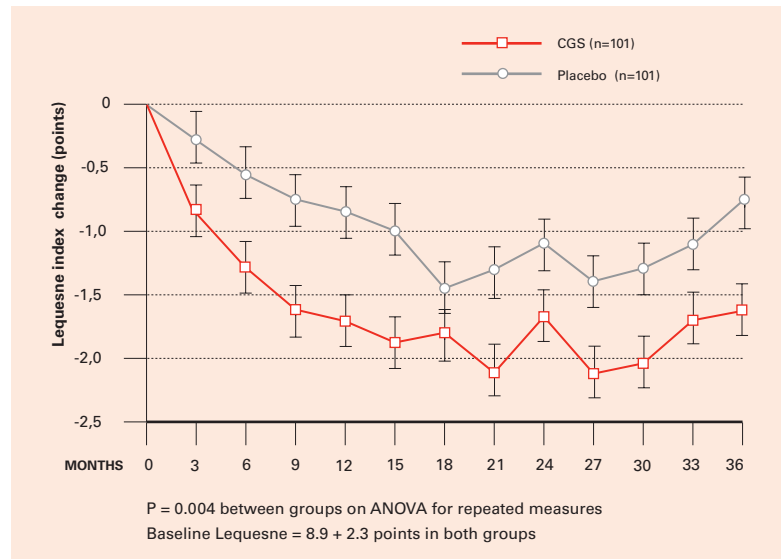
**FIGURE 17.**

Joint space narrowing (mean  $\pm$  SEM) in patients completing each year of the study. The number of evaluable patients in the placebo and CGS groups was 84 and 83, respectively, at year 1, 57 and 68 at year 2, and 55 and 65 at year 3

- Symptoms improved steadily over the first year of treatment with CGS, and this improvement was maintained until the end of the study (Figure 18).
- After 3 years, symptoms improved modestly with the placebo but as much as 20 to 25% with CGS. The effect size was similar to that observed in the first long-term study.

**FIGURE 18.**

Intent-to-treat population.  
Mean ( $\pm$ SE) change in the  
Lequesne index score at  
clinic visits throughout the  
study



## CONCLUSIONS

The two pivotal 3-year trials have shown, for the first time, that a pharmacological intervention can delay the progression of joint structure changes. In the editorial accompanying the first pivotal trial (The Lancet <sup>72</sup>), the author defined CGS as the possible dawn of a new era in the treatment of osteoarthritis, and the trial as a landmark in OA research.

Thus, combined symptom- and structure-modifying effects were obtained in two large, independent, randomized, placebo-controlled, long-term (3-year) trials, according to the regulatory requirements set forth in the CPMP/EWP/784/97 document <sup>11</sup>. This suggests that Glucosamine (in the form of CGS) may be the first disease-modifying agent in OA.

### 6.3 Studies Derived from the Pivotal Long-Term Trials

#### *Follow-up studies of patients who participated in the long-term trials 73,74,75*

These studies were undertaken to confirm that CGS positively affects the progression of osteoarthritis. In fact, if a drug has structure-modifying properties, long-term follow-up of patients should be able to document prevention of clinically significant disease outcomes—i.e., patient disability and/or the need for surgical joint replacement. Thus, patients who participated in the pivotal long-term studies were followed for an additional number of years after CGS was discontinued.

#### *Objective*

- To assess the incidence of total joint replacement in OA patients formerly receiving CGS or the placebo <sup>75</sup>.

#### *Methods*

- Patients participating in the two pivotal 3-year trials of CGS and receiving treatment for at least 12 months were contacted to participate in a long-term retrospective assessment of the incidence of total knee replacement.

#### *Results*

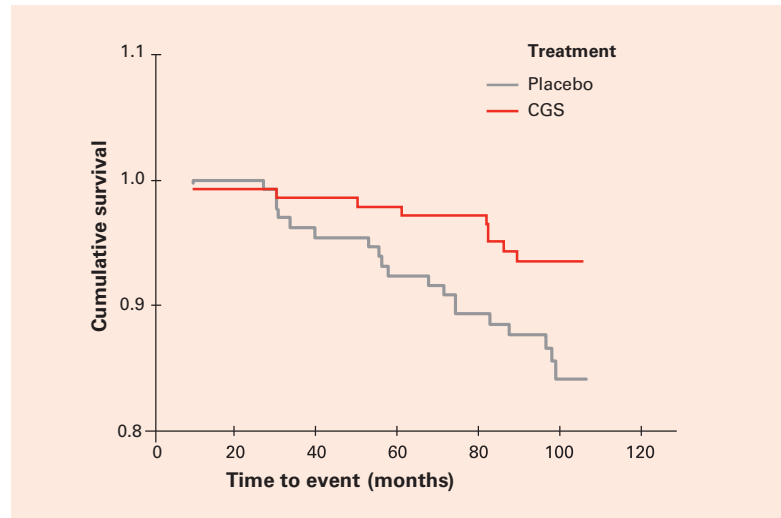
- Out of 340 patients with at least 12 months of treatment, 275 (81%) were retrieved and interviewed. There were no differences in baseline characteristics between groups.
- The mean duration of follow-up was about 5 years after treatment withdrawal. Thus, the mean period of observation was 8 years.
- Total knee replacement had occurred in over twice as many patients in the placebo groups (19/131, 14.5%) than in those in the CGS groups (9/144, 6.3%) ( $p=0.024$ ).
- The Kaplan Meier/Log-Rank test survival analysis confirmed a significantly decreased ( $p=0.026$ ) incidence of total knee replacements in patients who were formerly treated with CGS (Figure 19).

#### *Post-hoc analyses from the pivotal studies*

The publications summarized in this subsection have been derived from

**FIGURE 19.**

Time-to-event analysis:  
total knee replacement in  
the overall follow-up popu-  
lation (N=275):  $p=0.026$   
(Log-Rank test)



the pivotal long-term trials. They are important for a better understanding of the clinical effects of CGS.

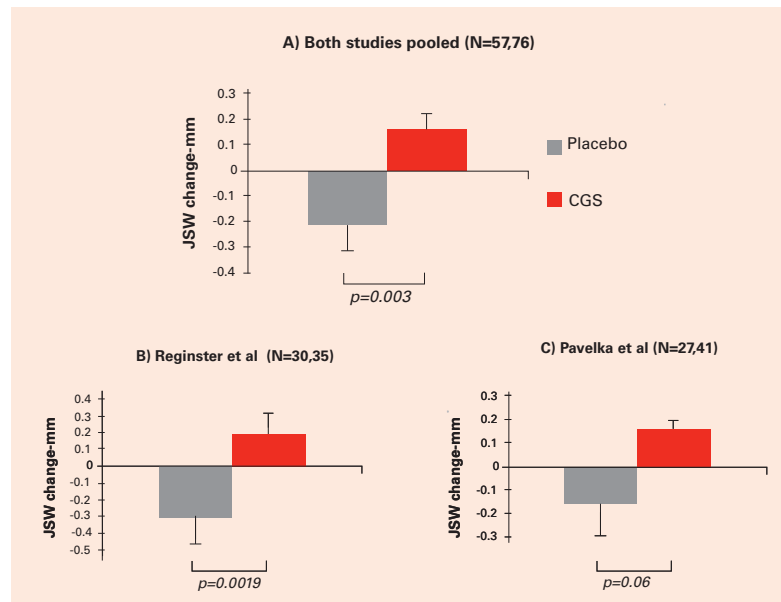
- Firstly, the post-hoc analysis of the predominant subgroup of post-menopausal women from the two 3-year trials, consisting of 319 patients, outlined a particularly evident symptom- and structure-modifying effect of CGS <sup>76</sup>. It should be noted that this population is the most frequently affected by knee OA.
- A second analysis <sup>77</sup> was carried out to assess whether the greater pain relief in the CGS arms could have
  1. altered the positioning of the knee;
  2. favored a better knee extension;
  3. confounded the estimate of JSN, exaggerating the differences between treatment groups.

To this end, patients completing the 3-year treatment course in either study were included in the analysis if their pain had improved at least as much as the mean improvement in the CGS arms. Patients meeting such a criterion were regarded as responders irrespective of treatment with CGS or placebo. This analysis demonstrated that pain relief did not confound the assessment of JSN at all (Figure 20), further validating the results of the studies designed to assess the efficacy of CGS as a structure-modifying drug in OA.



**FIGURE 20.**

Mean (SE) change in joint space width after 3 years. N represents the number of patients who qualified for the analysis (responders) in either group. The p values presented in the figure were obtained by analysis of variance. Analysis of covariance adjusting for baseline JSW gave p values of 0.002, 0.048 and 0.046 for panels A, B and C, respectively



Two additional full reports derived from post-hoc analyses of the pivotal trial by Reginster et al.<sup>56</sup>

- In the first one, the authors found a poor correlation between symptoms and radiographic findings<sup>78</sup>, as widely described in the literature. However, there was a modest but significant correlation between pain and JSN, and the symptom-modifying effect of CGS was significant regardless of baseline joint structural damage and its progression.
- Importantly, the results of the second analysis showed that patients with better preserved joint space at baseline suffered the most dramatic JSN after 3 years when receiving placebo and were those in whom the structure-modifying effect of CGS was more evident<sup>79</sup>. Such patients may be particularly responsive to structure-modifying drugs.

## CONCLUSIONS

**The structure-modifying effects of CGS are clinically relevant because treatment with CGS for up to 3 years decreases the incidence of total joint replacements, and this activity is real and not affected by confounders. Patients with better preserved joint space at baseline are those who benefit more from the structure-modifying properties of CGS. This finding has a broad significance and supports early intervention with CGS in patients with OA.**

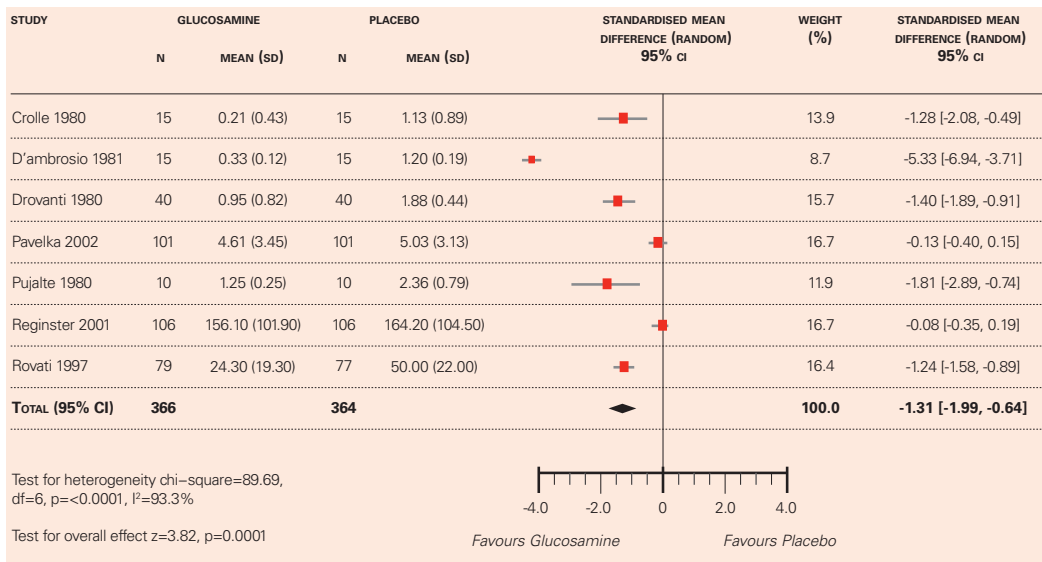
**With CGS, the Number Needed to Treat (NNT)—i.e., the number of patients that need to be treated to avoid one knee replacement—is 12.**

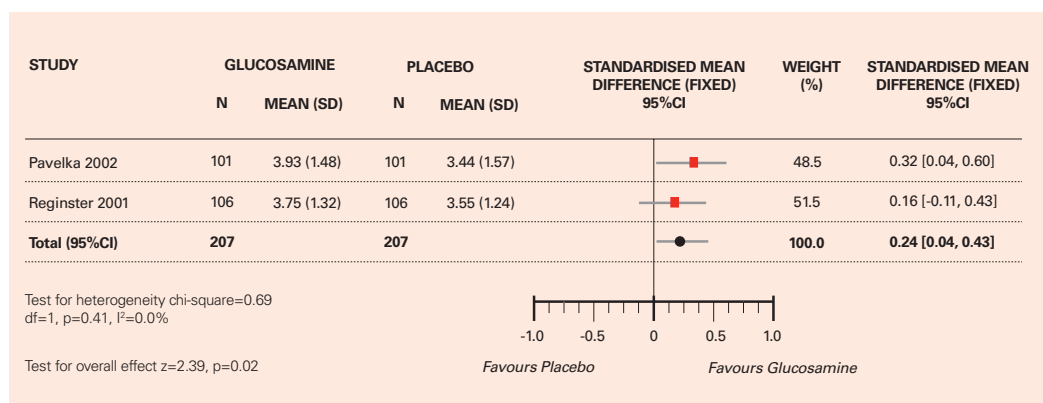
#### 6.4 Glucosamine therapy for treating osteoarthritis: the Cochrane Review

In the most recent version (2005) of the meta-analysis first published as a Cochrane Review in 2001<sup>80,25</sup>, all research was updated in January 2005. An additional four randomized controlled trials (RCTs; besides the 16 reviewed in the earlier version) were identified. The majority of the RCTs (13/20) had investigated the Glucosamine Sulfate manufactured by Rottapharm (i.e., CGS). Six RCTs did not use the Rottapharm preparation of Glucosamine, and one used both a non-Rottapharm and a Rottapharm preparation (in 90% and 10% of patients, respectively). Pooled results from studies using a non-Rottapharm preparation failed to show benefits in terms of pain and function, whereas those studies evaluating the Rottapharm preparation showed that CGS is superior to placebo in the treatment of pain (Figure 21) and functional impairment resulting from symptomatic osteoarthritis. In keeping with the results of the two pivotal long-term studies of CGS<sup>56,57</sup>, the Cochrane Review acknowledges that only the Rottapharm preparation of Glucosamine Sulfate may slow radiological progression of OA (Figure 22).

**FIGURE 21.**

From the Cochrane Review.  
Efficacy on pain: comparison of Glucosamine (Rottapharm preparation; CGS) versus placebo



**FIGURE 22.**

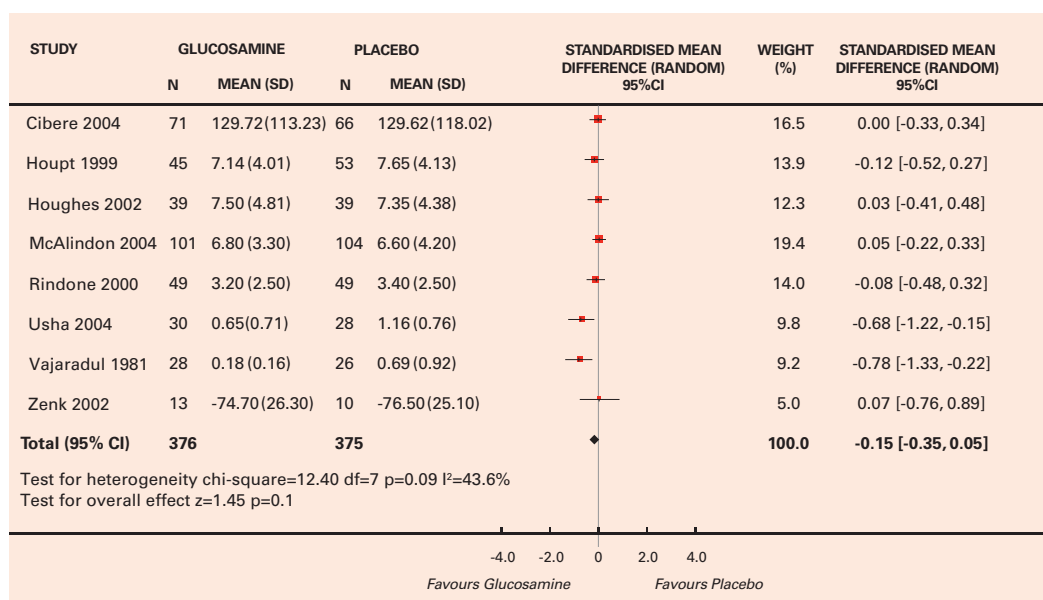
From the Cochrane Review.  
Minimum joint space width:  
comparison of Glucosamine  
(Rottapharm preparation;  
CGS) versus placebo

## 6.5 Clinical Studies With other Glucosamine Products and Combinations

As clearly outlined in the Cochrane Review, although the efficacy of Glucosamine can be documented when all available trials of any Glucosamine preparation are pooled together, the efficacy is linked only to the trials performed with Crystalline Glucosamine Sulfate (CGS, Rottapharm). Indeed, there is no symptom improvement in the pooled results of trials that used other Glucosamine preparations (Figure 23). This finding is important be-

**FIGURE 23.**

From the Cochrane Review.  
Pain: comparison of Gluco-  
samine (non-Rottapharm  
preparations) versus placebo



cause it comes from eminent, independent authors in a systematic summary of reliable evidence of the benefits and risks related to healthcare interventions.

All successful clinical studies of Glucosamine in the treatment of osteoarthritis have been conducted with the Crystalline form of Glucosamine Sulfate developed by Rottapharm. In the absence of

1. clinical trials directly comparing CGS with other forms of Glucosamine contained in generics or dietary supplements
  2. pharmaceutical similarity and/or human bioequivalence data,
- it is unacceptable to transfer the clinical benefits demonstrated for CGS to other claimed Glucosamine-derived compounds. Some of these products have been recently criticized for major deviations from label claims regarding the amount of active ingredient and, therefore, for poor pharmaceutical quality <sup>23,81</sup>. Moreover, most clinical trials with other forms of Glucosamine used a different dosage (500 mg three times daily instead of 1500 mg once daily). As detailed in the Pharmacokinetics section, doses lower than 1500 mg are very unlikely to produce plasma and synovial fluid concentrations of Glucosamine in the 10 µM range—i.e., those required to inhibit the effects of IL-1 <sup>41</sup>.

#### ***6.5.1 Non-Rottapharm preparations of Glucosamine Sulfate (potassium salts)***

Potassium salts of Glucosamine Sulfate are not effective in relieving the symptoms of osteoarthritis. In addition, quality and design issues have been identified in some studies where potassium salts of Glucosamine Sulfate were used <sup>82</sup>.

For instance, the trial by Cibere et al. <sup>83</sup> allocated >30% of patients to ≤1000 mg/day of Glucosamine Sulfate, a dosage that is one-third lower than the approved dosage of 1500 mg/day. The study was underpowered (<70 patients/group), and there were imbalances in baseline patient characteristics in favor of the placebo. Moreover, the randomized discontinuation design used in this trial is inadequate for drugs with a carryover effect such as Glucosamine <sup>14</sup>. In fact, nearly 60% of the patients did not flare during the 6 months after the open-label run-in phase with Glucosamine.

The trial by Hughes and Carr <sup>84</sup> was undersized (40 patients/group), and its validity was further challenged by the high proportions of patients continuing their NSAID/analgesic medications, with a strong placebo response.

### 6.5.2 Glucosamine hydrochloride alone or in combination with chondroitin sulfate

Glucosamine hydrochloride (G-HCl) 500 mg 3 times daily, alone or in combination with chondroitin sulfate, is not effective in controlling either OA symptoms or disease progression. This is clear from the results of the 2 high-quality trials carried out with this Glucosamine formulation: the study by Houpt et al.<sup>85</sup> and the recent NIH-sponsored Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT)<sup>54,86</sup>.

Houpt et al. did a randomized, placebo-controlled, 8-week, good quality trial. However, the statistical power of the study was limited, with a total sample size of only 118 patients with knee osteoarthritis. Although positive trends were found for the G-HCl group in most WOMAC questions, the primary endpoint (a significant difference in WOMAC pain score) was not met.

The NIH-sponsored GAIT trial, a large clinical study including 1583 patients with symptomatic knee osteoarthritis, was recently completed<sup>54</sup>. Patients were randomly assigned to receive Glucosamine hydrochloride (G-HCl; 500 mg 3 times daily), chondroitin sulfate (CS; 400 mg 3 times daily), both G-HCl and CS, celecoxib (200 mg daily), or a placebo for 24 weeks. The primary endpoint was a 20% decrease in the WOMAC pain subscale from baseline to week 24. There was a high rate of response to the placebo (60%), most probably due to the uncontrolled use of the rescue analgesic medication. Overall, Glucosamine hydrochloride and chondroitin sulfate, alone or in combination, were not significantly better than placebo in reducing knee pain (Table 12).

A 24-month study was carried out as part of the GAIT trial to evaluate the effects of Glucosamine hydrochloride and chondroitin sulfate (alone or

**TABLE 12.**  
GAIT trial: primary outcome measure

Outcome	Placebo	G-HCl	CS	G-HCl + CS	Celecoxib
Randomized patients	313	317	318	317	318
Patients who met the primary endpoint*					
• N (%)	188 (60.1)	203 (64.0)	208 (65.4)	211 (66.6)	223 (70.1)
• P vs. placebo	-	0.30	0.17	0.09	0.008†

\*Defined as a 20% decrease in the summed score for the WOMAC pain subscale;

†, significant effect vs. placebo

in combination), celecoxib, and placebo on the progression of OA<sup>86</sup>. The final sample comprised 357 patients, and the primary endpoint was the mean change in joint space width (JSW) from baseline. Similar to what had been observed for symptoms, no significant differences were observed between the placebo group and the groups receiving Glucosamine hydrochloride, chondroitin sulfate, or a combination of the two (Table 13).

Treatment	Subjects assessed, N	Mean JSW loss over 2 years, mm	Progression* % of patients
G-HCl	77	0.013†	18.6†
CS	71	0.107†	21.4†
G-HCl + CS	59	0.194†	24.4†
Celecoxib	80	0.111†	20.2†
Placebo	70	0.166	22.4

\*Progression was defined as JSW loss exceeding 0.48 mm  
† NS vs placebo

**TABLE 13.**

GAIT trial: loss of JSW and disease progression over 2 years

As the accompanying editorial states, the negative findings of the GAIT trial are not surprising, given the Glucosamine product used in this study. In fact, all the favorable trials previously conducted featured the use of with the prescription drug Crystalline Glucosamine Sulfate<sup>87</sup>. **Then the editorial continues with the recommendation that if patients choose to take Glucosamine to control their symptoms, they should be advised to take Glucosamine Sulfate rather than Glucosamine hydrochloride.** This recommendation is supported not only by clinical evidence but also by mechanistic and pharmacokinetic studies, because G-HCl 500 mg three times daily has a different Pharmacokinetic/Pharmacodynamic profile than CGS 1500 mg once daily. As described in the Pharmacokinetics section, the peak Glucosamine plasma levels achieved with the hydrochloride formulation used in GAIT are much lower than those achieved with the prescription sulfate formulation (CGS) used in GUIDE<sup>55</sup>. Such lower peak plasma concentrations might not reach the pharmacologically effective threshold, which could explain the lack of efficacy of Glucosamine hydrochloride in OA. In addition, sulfates have been suggested as an important component of the CGS mechanism of action<sup>42</sup>, and Glucosamine Sulfate is a stronger inhibitor of gene expression than Glucosamine hydrochloride<sup>43</sup>.

The role of sulfate ions extends the discussion to the lack of efficacy of Glucosamine combined with chondroitin sulfate in the management of

OA. Chondroitin sulfate is a glycosaminoglycan normally present in the cartilage matrix. More specifically, it is a high-molecular-weight chain of sulfated residues of glucuronic acid and N-acetyl-galactosamine, obtained by extraction processes from animal tissues. Chondroitin sulfate is used for treating osteoarthritis based on a rationale that is speculatively similar to that of Glucosamine Sulfate, which is difficult to understand given the major differences in their physicochemical properties. Although oral absorption of chondroitin sulfate cannot be excluded, pharmacokinetics studies have shown that the largest peak consists of N-acetyl-galactosamine monomers<sup>88</sup>. Thus, N-acetyl-galactosamine is probably responsible for the pharmacological activity of chondroitin sulfate. Consistent with this hypothesis, early studies showed that N-acetyl-galactosamine may induce metabolic activities similar to those of its precursor Glucosamine, although with a lower potency<sup>89</sup>. It may be speculated that the clinical activity reported for chondroitin sulfate in some clinical trials may be similar to that of Glucosamine Sulfate at low doses.

Anecdotal evidence claims that combining chondroitin sulfate and Glucosamine may offer added value in the treatment of osteoarthritis. However, there is no scientific proof for this claim and, based on the facts presented, the rationale for such a combination is also weak. This is particularly true when it comes to dietary supplements. Indeed, research from the University of Maryland has recently detected major deviations from label claims for several of these products<sup>81</sup>.

In line with the above arguments, the GAIT trial showed that the combination of Glucosamine hydrochloride and chondroitin sulfate is not effective in patients with osteoarthritis—not effective on symptoms, not effective on structural changes. Again, this finding is supported by pharmacokinetic studies, because chondroitin sulfate reduces the bioavailability of Glucosamine<sup>55</sup> (Table 14).

**TABLE 14.**

Mean ( $\pm$ SD) plasma Glucosamine levels after the administration of CGS, G-HCl, and G-HCl in combination with CS

	CGS	G-HCl	G-HCl + CS
Peak plasma concentration (ng/mL)	1623.6 $\pm$ 1131.6†	798.4 $\pm$ 317.3	588.9 $\pm$ 181.5
Peak plasma concentration ( $\mu$ M)	9.1 $\pm$ 6.3†	4.5 $\pm$ 1.8	3.3 $\pm$ 1.0
CGS, 1500 mg once daily; G-HCl, 500 mg 3 times daily; and G-HCl in combination with CS, 500 mg + 400 mg, respectively, 3 times daily; †p<0.05 vs. G-HCl and vs. G-HCl +CS.			

#### CONCLUSIONS

Glucosamine products other than CGS do not provide either symptom- or structure-modifying effects in patients with OA. This finding is consistent with the results from mechanistic and pharmacokinetic studies. For instance, the peak Glucosamine plasma levels achieved with Glucosamine hydrochloride 500 mg three times daily (used in the GAIT trial—negative results) are much lower than those reached with CGS (used in the GUIDE trial—positive results). Such lower concentrations might not reach the pharmacologically effective concentration.

There is no evidence, or rationale, for combining Glucosamine with chondroitin sulfate. Moreover, chondroitin sulfate reduces the bioavailability of Glucosamine.



## CHAPTER 7

# Crystalline Glucosamine Sulfate Safety and Tolerability

All trials, reviews, and meta-analyses recognize the good safety profile of Crystalline Glucosamine Sulfate (CGS) and Glucosamine in general. There are no statistically or clinically significant differences between CGS and placebo in the incidence of adverse events or safety-related withdrawals.

Although at a significantly lower frequency and severity than with conventional NSAIDs, adverse events with CGS seem to be mostly related to the gastrointestinal (GI) system and consist of mild, transient episodes of abdominal pain, nausea, dyspepsia, diarrhea, or constipation.

### 7.1 Safety in Short-Term Trials

The safety profile of CGS was good in all short-term (supportive) clinical trials, in which the drug was compared with a placebo or NSAIDs.

Noack et al.<sup>63</sup> report that tolerability was similar between CGS and placebo, with a 6% incidence of minor adverse events in the CGS group and 10% in the placebo group. Routine laboratory tests at entry and on study completion did not show any clinically significant changes.

According to Müller-Faßbender et al.<sup>66</sup>, CGS was significantly better tolerated than ibuprofen, with adverse events reported in 6% of patients compared with 35% with ibuprofen ( $p < 0.001$ ). A related discontinuation rate of only 1% was reported for CGS, compared with 7% for ibuprofen ( $p = 0.035$ ). No clinically significant laboratory changes were observed.

In the study by Rovati<sup>68</sup>, the incidence of treatment-emergent adverse

**TABLE 15.**

GUIDE Trial. Summary of adverse events occurring in at least 3 patients/group during treatment\*

(\*Adverse events were grouped by system organ class and reported as Medical Dictionary for Regulatory Activities [MedDRA] lower-level term except for respiratory tract infections and respiratory disorders, for which similar events were grouped under MedDRA high-level term)

events in patients receiving CGS was similar to that of the placebo group ( $p=0.16$ ) and significantly lower than that of the piroxicam group (15% vs. 42%,  $p<0.001$ , with 9% vs. 33% referred to the GI tract).

## 7.2 Safety in Pivotal (Medium- and Long-Term) Trials

In the pivotal, medium-term (6-month duration) GUIDE trial<sup>58</sup>, the number of adverse events was similar in the three groups: 89 with placebo, 96 with acetaminophen, and 95 with CGS. The most frequent adverse events were of minor clinical significance and did not differ in frequency between groups. Table 15 summarizes the adverse events reported by at least 3 patients/group. There were 5 serious adverse events in the placebo group (precordial chest pain, apnea, pneumonia, elective surgery, and lumbar pain), 5 in the acetaminophen group (atrial flutter, carpal tunnel syndrome,

	Events, N		
	Placebo	Acetaminophen	CGS
<b>Gastrointestinal disorders</b>			
Dyspepsia	4	2	5
Abdominal pain	4	4	3
Diarrhea	4	4	3
<b>Infections</b>			
Respiratory tract infections	9	4	8
Gastroenteritis	2	0	4
<b>Respiratory disorders</b>			
Coughing and associated symptoms	0	4	1
<b>Nervous system disorders</b>			
Headaches	4	6	2
Dizziness	1	4	1
<b>Musculoskeletal disorders</b>			
Back pain	5	4	7
Neck pain	0	2	3
<b>Injuries</b>			
Fall	2	3	5
Injury	0	4	2

vertebral fracture, meniscus rupture, and crush injury), and 2 in the CGS group (meniscus rupture and elective surgery). The side comparator acetaminophen was also well tolerated. However, even if the drug was used at a relatively low dosage (3 g/day), abnormalities in liver function [as reflected by levels of transaminases and gamma glutamyl transferase (GGT)] were found in approximately 20% of the acetaminophen-treated patients vs. 6% and 2% in the placebo and CGS groups, respectively.

Pivotal long-term trials provided a unique opportunity to evaluate the safety of CGS during prolonged and continuous use in patients with osteoarthritis, which is seldom, if ever, described for other medications currently indicated for this disease.

In both the 3-year studies, CGS and placebo were similarly tolerated. Given the different study design compared with the short-term studies (i.e., a long-term continuous administration in elderly subjects), most patients in either group reported at least one adverse event: 94% and 93% with CGS and placebo, respectively, in the study by Reginster et al.<sup>56</sup>; 66% and 64%, respectively, in the study by Pavelka et al.<sup>57</sup>. However, the safety pattern was similar to that described in short-term studies, with transient, mild-to-moderate adverse events in both groups.

Table 16 shows the frequencies of the most common adverse events recorded in the study by Reginster et al.<sup>56</sup>. In about half the cases, these events were referred to the GI system and maybe also referred to the rescue medication, without differences between groups. Adverse events caused early withdrawal in 17% of patients receiving placebo and 20% of those receiving CGS ( $p=0.72$ ). Among adverse events leading to drug discontinuation, few single episodes were serious. These were all judged as unrelated to the study treatment, mostly because such episodes were attributable to concomitant conditions, without significant differences between CGS and the placebo.

Laboratory tests did not show clinically significant abnormalities. Also, there was no change in glycemic homoeostasis. Fasting plasma glucose concentrations decreased slightly in the CGS group.

**TABLE 16.**

Proportions of patients reporting adverse events (frequency  $\geq 5\%$ ) in the pivotal long-term trial by Reginster et al.

Adverse event*	Placebo (n=106)	CGS (n=106)
Abdominal pain	18 (17%)	13 (12%)
Dyspepsia	8 (8%)	4 (4%)
Diarrhea	11 (10%)	10 (9%)
Increased blood pressure	15 (14%)	15 (14%)
Decreased blood pressure	8 (8%)	2 (2%)
Cardiac failure	7 (7%)	4 (4%)
Fatigue	7 (7%)	10 (9%)
Headache	4 (4%)	6 (6%)
Vertigo	3 (3%)	7 (7%)
Neuritis	6 (6%)	4 (4%)
Depressive mood	7 (4%)	4 (6%)
Allergic episode	7 (7%)	4 (4%)
*Seasonal/infective upper respiratory tract disorders were reported by 49% of patients on placebo and 51% of patients on CGS; influenza-like symptoms were reported by 23% and 28% of patients on placebo and CGS, respectively.		

Similar results were reported in the second pivotal long-term trial<sup>57</sup>, with no statistically significant differences between groups in the proportion or pattern of adverse events (Table 17). Musculoskeletal reports were mainly caused by OA-related symptoms or back pain. Cardiovascular events consisted mainly of episodes of increased blood pressure or recurrent manifestations of preexisting cardiovascular disease. As expected, a high proportion of patients reported seasonal upper respiratory tract infections. Urinary tract infections were also common. Four patients developed clinically evident diabetes mellitus during the study (3 were taking placebo [1 dropout] and 1 was taking CGS). Routine laboratory tests did not show significant differences between groups.

**TABLE 17.**

Patients reporting at least 1 adverse event during the 3-year study by Pavelka et al., by body system\*  
 (\*Each patient may have reported >1 adverse event in the same or other organ classes. WHO, World Health Organization.)

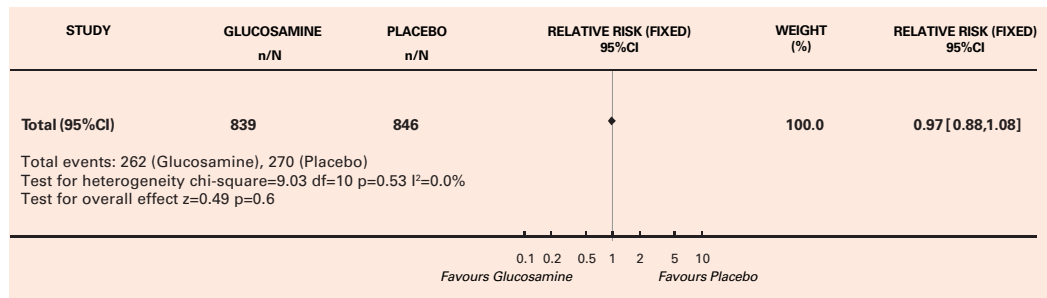
<b>System organ class (WHO coding)</b>	<b>Placebo, % (n=101)</b>	<b>CGS, % (n=101)</b>
GI tract and liver	28	25
Musculoskeletal	22	30
Cardiovascular	20	23
Skin and appendages	15	10
Respiratory tract	7	17
Urinary tract	11	12
Metabolic and nutritional	6	7
Other †	14	14

†Includes isolated adverse events in the following systems: nervous, psychiatric, blood cell disorders, neoplasm, endocrine disorders, reproductive (male/female), vision disorders, hearing, and vestibular.

### 7.3 Reviews and Guidelines Assessing the Safety Profile of Glucosamine

According to the most recent Cochrane Review <sup>25</sup>, the safety profile of Glucosamine in the 20 RCTs assessed was excellent. CGS was used in most studies. Of the 1160 patients randomized to Glucosamine, only 4% were withdrawn because of toxicity, and the proportion of subjects reporting an adverse reaction was 26% based on 17 RCTs. Among the subjects randomized to a placebo group, 5% were withdrawn because of toxicity and 32% reported an adverse reaction. Hence, Glucosamine proved to be as safe as the placebo. When Glucosamine was compared to the placebo in terms of the number of subjects reporting adverse reactions, the summary relative risk (RR) for 14 RCTs was 0.97 (95% CI, 0.88-1.08; Figure 24).

The incidence of adverse events in comparative clinical trials was always significantly higher with NSAIDs than with CGS (Figure 25). The majority of adverse events in NSAID-treated patients were obviously referred to the GI tract. Unlike conventional NSAIDs, Glucosamine does not inhibit

**FIGURE 24.**

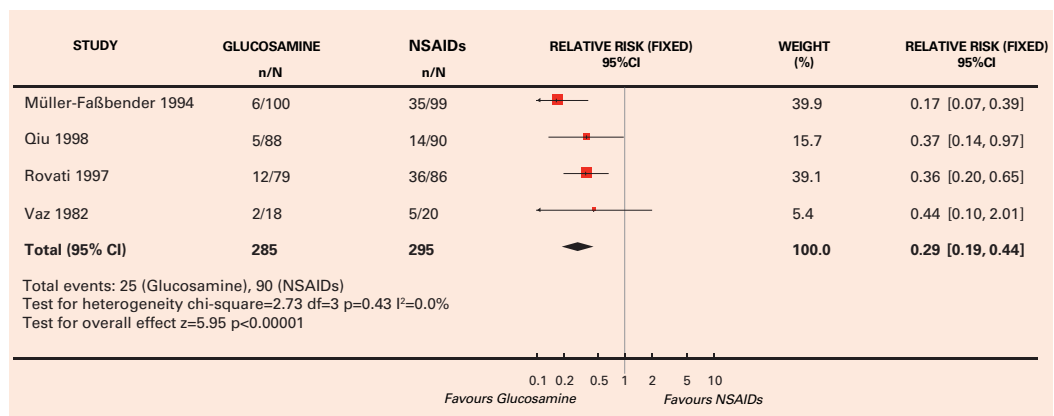
From the Cochrane Review.  
Comparison of Glucosamine  
(CGS + other preparations)  
versus placebo: number of  
patients reporting adverse  
events

type 1 cyclooxygenase (COX-1), which explains the better safety pattern at the GI level. The few GI events observed with CGS were similar to those reported with placebo. Because neither CGS nor obviously the placebo has the potential to cause specific GI problems, the adverse events observed with CGS may be related to the general discomfort that arises with any oral drug intake in some patients. Furthermore, OA patients are accustomed to the well-known GI side effects of symptomatic medications such as NSAIDs, and they may be more likely to report such events.

The overall safety profile of CGS in the main short-term trials and in the pivotal trials (with the exclusion of the GUIDE study; see Table 15 for details on the latter) was summarized in a recent review<sup>90</sup>. Table 18 reports the proportion of patients with adverse events and the rate of withdrawals due to adverse events. Overall, adverse events occurred in less than 15% of patients participating in the short-term studies. After long-term exposure, the incidence of adverse events was higher but identical to that of the placebo.

**FIGURE 25.**

From the Cochrane Review.  
Comparison of CGS versus  
NSAIDs [piroxicam, ibuprofen]:  
number of patients  
reporting adverse events



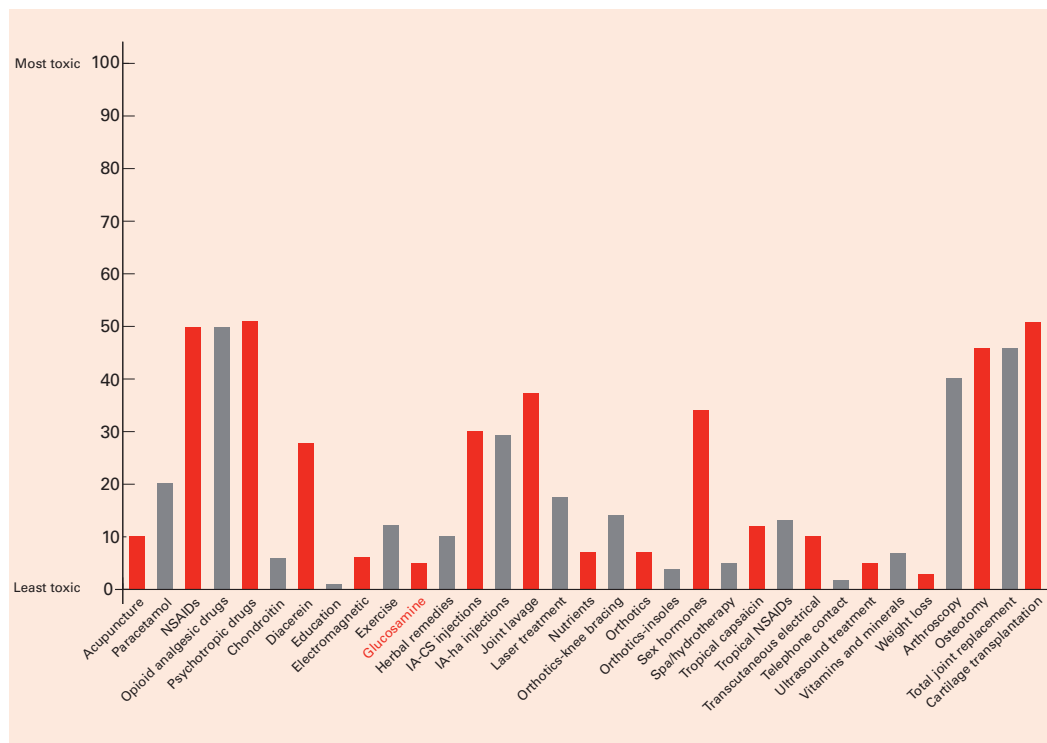
Study	Groups	Patients with AE (%)	Patients withdrawn due to		
			AE (%)	Lack of efficacy (%)	Other reasons (%)
Noack <sup>63</sup>	Placebo (n=126)	10.3	6.3	0.0	1.6
	CGS (n=126)	6.3	4.0	0.0	2.4
	p: CGS vs. placebo	NS	NS	-	-
Müller-Faßbender <sup>66</sup>	Ibuprofen (n=99)	35.4	7.1	1.0	4.0
	CGS (n=100)	6.0	1.0	1.0	0.0
	p: CGS vs. ibuprofen	<0.001	0.035	-	-
Rovati <sup>68</sup>	Placebo (n=77)	24.7	5.2	7.8	10.4
	CGS (n=79)	15.2	0.0	1.3	1.3
	Piroxicam (n=86)	41.9	20.9	3.5	8.1
	Combination* (n=77)	36.4	2.6	0.0	3.9
	p: CGS vs. placebo	NS	NS	-	-
	p: CGS vs. piroxicam	<0.001	<0.001	-	-
	p: CGS vs. combination	0.003	NS	-	-
	p: piroxicam vs. combination	NS	0.003	-	-
Reginster <sup>56</sup>	Placebo (n=106)	93	17.0	4.7	11.3
	CGS (n=106)	94	19.8	2.8	13.2
	p: CGS vs. placebo	NS	NS	-	-
Pavelka <sup>57</sup>	Placebo (n=101)	64	9.9	5.0	30.7
	CGS (n=101)	66	7.9	7.9	18.8
	p: CGS vs. placebo	NS	NS	-	-
Statistical analysis by the two-tailed $\chi^2$ or Fisher exact test, as appropriate. NS=not significant				*CGS plus piroxicam	

**TABLE 18.**

CGS high-quality trials:  
proportions of patients with  
adverse events (AE) and of  
withdrawals

**FIGURE 26.**  
From the most recent  
EULAR Guidelines on  
knee OA. Toxicity profile of  
the treatment modalities  
based on expert opinion (23  
experts)

In preparing the EULAR recommendations for the management of knee OA <sup>16</sup>, the members of the expert committee also analyzed the toxicity of pharmacological and non-pharmacological interventions. Once the list of treatments had been completed, the committee ranked the potential toxicity of each intervention on a 100 mm visual analogue scale (0-not toxic at all; 100-very toxic). Figure 26 shows the results obtained. NSAIDs, opioid analgesics, and antidepressant drugs were regarded as having a toxicity profile similar to that of joint replacement surgery. Conversely, Glucosamine scored less than any other pharmacological treatment and was rated as similar to harmless interventions such as hydrotherapy, for instance.



## 7.4 Safety in Special Groups and Situations

### *Impaired glucose tolerance*

Because Glucosamine is an amino monosaccharide, it was speculated that it might interfere with the hexosamine pathway, thus leading to hyperglycemia and insulin resistance. However, the hypothetical mechanisms of



Glucosamine-induced alterations of glucose metabolism have never been observed in humans. Conversely, several studies have demonstrated that therapeutic doses of CGS do not influence glucose metabolism.

The possibility that exogenous Glucosamine might alter glucose metabolism in humans was raised following experimental studies in which very large amounts of Glucosamine were infused intravenously into rats<sup>91,92</sup>. Under these conditions, Glucosamine tended to decrease insulin secretion and/or induce insulin resistance in peripheral tissues. In contrast, other animal studies did not find any adverse effects of Glucosamine on blood glucose<sup>93</sup>, not even in models highly sensitive to sugar-induced insulin resistance<sup>94</sup>.

At least two studies have investigated the effect of intravenous or intra-arterial Glucosamine infusion in healthy human volunteers<sup>95,96</sup>. Unlike the experimental models, these studies do not support a role for Glucosamine and the hexosamine pathway in the regulation of insulin sensitivity in humans, at least over the short-term but at much higher concentrations than those observed after therapeutic doses of CGS. A further physiology study assessed whether repeated administration of a therapeutic dose (1500 mg/day) of GS could induce glucose intolerance<sup>97</sup>. Nineteen healthy adults received the treatment for 12 weeks. There were no alterations in serum insulin or blood glucose during an oral glucose tolerance test (OGTT) performed after 6 and 12 weeks of treatment. Similarly, there were no changes in glycated hemoglobin levels.

Scroggie et al. examined whether treatment with Glucosamine could affect preexisting diabetes<sup>98</sup>. Twenty-six patients with controlled type 2 diabetes received a combination of Glucosamine 1500 mg and chondroitin sulfate 1200 mg for 90 days, whereas 12 patients received a placebo. There were no significant changes within or between groups in glycated hemoglobin levels, indicating that oral Glucosamine does not alter glucose metabolism in patients with mild and well controlled type 2 diabetes.

Several clinical studies have now demonstrated that CGS does not affect fasting plasma glucose levels. This was initially reported in a correspondence to *The Lancet*<sup>99</sup> with reference both to a short-term (4-week) clinical trial including a small subset of patients with hyperglycemia at baseline<sup>63</sup> and to the long-term study by Reginster et al.<sup>56</sup>, in which fasting blood glucose tended on average to decrease. The possibility that chronic administration of CGS could induce the onset of diabetes was also exclu-

ded in the long-term clinical trial by Pavelka et al.<sup>57</sup> Four patients developed diabetes during the 3-year study, but 3 were on placebo and only 1 on CGS.

Fasting glucose levels were also measured in the recent pivotal GUIDE trial<sup>58</sup>. Table 19 shows that mean serum glucose levels were virtually unaltered in all treatment groups between screening and the 3- or 6-month assessment.

	Absolute serum glucose values (mg/dL)		
	CGS	Acetaminophen	Placebo
Screening	98.06 ± 15.37 (n=98)	99.25 ± 13.21 (n=102)	98.69 ± 14.39 (n=100)
3 Months	96.53 ± 14.98 (n=80)	100.02 ± 17.99 (n=84)	100.86 ± 15.97 (n=83)
6 Months	97.94 ± 14.62 (n=80)	99.56 ± 14.33 (n=75)	101.84 ± 15.97 (n=75)

**TABLE 19.**

GUIDE trial. Mean ± SD serum glucose levels (n is the number of patients whose serum glucose value was available at each time point)

To determine whether therapeutic doses of CGS could worsen glycemic control in hyperglycemic subjects, those with serum glucose levels above the Upper Normal Limit (UNL) at screening were examined in a separate analysis. CGS did not worsen glycemic control in this subgroup of patients. On the contrary, mean serum glucose levels tended to decrease with time (Table 20). Similar results were observed in the subset of patients treated with acetaminophen, whereas glucose levels were unaffected in the placebo group.

Overall, a growing body of evidence seems to exclude that Glucosamine (any dose or formulation, and independent of treatment duration) may affect glucose metabolism in humans. The absence of risk in this respect has been endorsed by two recent Glucosamine reviews<sup>100,101</sup>. However, data on diabetic patients are limited and virtually absent for chronic treatments in patients with severe or uncontrolled diabetes. Until further information becomes available, it is suggested that patients with impaired glucose tolerance have their blood glucose levels monitored when starting CGS therapy.

	Absolute serum glucose values (mg/dL)		
	CGS	Acetaminophen	Placebo
Screening (n=tot pts, pts>UNL)	128.83 ± 16.67 (n=12, 12)	119.88 ± 10.37 (n=17, 17)	124.13 ± 12.16 (n=15, 15)
3 Months (n=tot pts, pts>UNL)	121.70 ± 21.65 (n=10, 7)	115.75 ± 16.18 (n=16, 8)	125.50 ± 14.11 (n=14, 12)
6 Months (n=tot pts, pts>UNL)	119.60 ± 20.17 (n=10, 7)	115.71 ± 13.78 (n=14, 7)	124.64 ± 14.73 (n=14, 12)

n=tot pts: the number of patients with an abnormal serum glucose value at baseline and, of these, the number of patients for whom serum glucose levels were available after 3 and 6 months.  
n=pts>UNL: number of patients with a serum glucose level above UNL

**TABLE 20.**

GUIDE trial. Mean ± SD serum glucose levels of patients with glycemia >UNL at screening (UNL value was 110 mg/dL, as established by the American Diabetes Association in August 2005)

Based on *in vitro* and animal data, the once daily dose of CGS produces peak plasma levels sufficient to attain efficacy in OA but largely insufficient to potentially affect glucose metabolism. In cultured L6 cells, Glucosamine influences glucose uptake at concentrations higher than  $5 \times 10^{-3}$  M, whereas no effect is observed at lower concentrations (i.e.,  $10^{-3}$  and  $10^{-4}$  M) <sup>102</sup>. When CGS is administered to healthy subjects at normal therapeutic doses (equivalent to GS 1500 mg), it provides a mean maximum plasma concentration ( $C_{\max}$ ) of  $9 \times 10^{-6}$  M. At 3000 mg/day—twice the normally prescribed therapeutic dose—the maximum plasma concentration at steady state is  $1.4 \times 10^{-5}$  M <sup>50</sup>.

### Allergy

Glucosamine is mostly obtained from shellfish. For this reason, people with a shellfish allergy may be more susceptible to allergic reactions when taking Glucosamine of shellfish origin. In one study, Glucosamine Sulfate was administered to patients suffering from a shellfish allergy and was found not to cause allergic reactions or result in positive skin prick tests <sup>103</sup>. The author concluded that Glucosamine is probably safe for patients with a shellfish allergy.

It should be emphasized that CGS is produced in a way that minimizes or removes the potential residual protein content. Therefore, cross-reactions in patients with seafood allergies are unlikely. However, considering the possible consequences of an allergic reaction for hypersensitive patients, physicians should advise patients with a known shellfish allergy to take CGS with caution.

#### *Renal or hepatic insufficiency*

No special studies have been done in patients with renal or hepatic insufficiency. The toxicological/pharmacokinetic profile of CGS does not indicate limitations for these patients. However, CGS should be administered to subjects with severe hepatic or renal insufficiency under medical supervision.

### **7.5 Interactions With other Drugs and other Forms of Interaction**

Osteoarthritis is a chronic disease that mostly affects elderly patients who may be receiving treatments for other concomitant diseases. Glucosamine does not compete for absorption mechanisms and does not bind to plasma proteins. The metabolic fate of this endogenous substance is mainly incorporation into proteoglycans or metabolism independent of the cytochrome enzyme system. Therefore, although no formal drug interaction studies have been reported, the physicochemical, pharmacokinetic, and metabolic properties of Glucosamine suggest a low potential for drug interactions.

One exception is the possible interaction between Glucosamine and oral anticoagulants (e.g., warfarin, acenocoumarol). Some case reports and one letter have been found in the literature<sup>104,105,106,107</sup>. The retrieved articles indicate an unclear pharmacodynamic mechanism of interaction between Glucosamine and oral anticoagulants. Because the majority of reports draw attention to an increased INR, the most likely signal of altered coagulation seems to be, if confirmed, a slightly diminished coagulation. Although more information is necessary to define this interaction, patients should be advised that the concomitant use of Glucosamine and oral anticoagulants may increase the INR.

Finally, the sodium content of oral formulations (151 mg for the 1500

mg daily dose) should be taken into account by patients on a controlled sodium diet.

#### CONCLUSIONS

**Oral CGS 1500 mg once daily is an optimal dosage also from a safety point of view. The incidence of adverse events and related withdrawals is similar to that of the placebo and significantly better than that of conventional NSAIDs. The low proportion of adverse events consists mainly of mild and transient GI symptoms.**

**Therapeutic doses of CGS do not affect glucose levels. Moreover, because CGS does not interfere with absorption mechanisms and is not metabolized by the cytochrome P450 system, the potential for interaction with other drugs is very low.**



## CHAPTER 8

# Crystalline Glucosamine Sulfate Pharmacoeconomics

The socioeconomic impact of osteoarthritis is becoming more significant as the age of the general population increases, because this disease occurs mainly in subjects over 50 years of age. The following characteristics further exacerbate the impact of osteoarthritis on the community:

- OA is common
- OA can affect anyone
- OA is associated with considerable morbidity.

Thus, when treating osteoarthritic patients, attention should be paid to pharmacoeconomic aspects.

In a cost-benefit analysis of a 3-month treatment of patients with knee OA, CGS compared favorably with piroxicam. The use of CGS resulted in a potential net saving of 11 Euro/patient in 90 days and 110 Euro/patient in 150 days. These figures were calculated based on the value of the Euro in the year 2000<sup>108</sup>. Regardless of the positive results, this analysis did not take into account the benefits derived from the long-term effects of CGS. A more accurate pharmacoeconomic evaluation of CGS could be obtained during the follow-up of patients participating in the two pivotal long-term trials.

### 8.1 Pharmacoeconomic considerations based on the pivotal long-term trials

A recent study<sup>75</sup> assessed the incidence of total joint replacement (TJR) during the long-term follow-up of the knee OA patients who had for-

merly received CGS or a placebo during the two 3-year pivotal trials<sup>56,57</sup>. The populations from the two cohorts were merged for the purpose of this particular analysis. To make the findings more accurate and clinically relevant, only those patients who had received the treatments for at least 12 months were included in the analysis. The authors retrieved 81 % of these patients—i.e., a total of 275 patients (131 formerly on placebo and 144 formerly on CGS)—and interviewed them regarding the occurrence of total knee replacement. Patients had stopped the study treatments at the end of the trials and had moved to a standard of care for an average of 5 years after trial completion (for a total of 2178 patient-years of observation).

Nineteen of the 131 (14.5%) patients formerly on placebo had undergone TJR during the follow-up, compared with only 9/144 (6.3%) ( $p=0.024$ ) of those formerly receiving CGS. The relative risk was 0.43 (95% CI: 0.20 to 0.92). Patients who had received CGS 1500 mg once daily for at least 12 months and up to 3 years during the trials therefore had a 57% lower risk of undergoing TJR in the following 5 years.

If such data are included in any pharmacoeconomic model, the cost-effectiveness of long-term treatment with CGS would be highly favorable under any circumstances.

Despite these data, that speak for themselves, the authors also did a standard pharmacoeconomic assessment based on the last year of follow-up. The analysis was performed in a subset of 101 patients who had undergone a clinic visit and could be administered a detailed questionnaire on the use of health resources. The questionnaire included the use and cost (based on national formulary reference prices where the analysis was undertaken) of:

- medications
- OA-related visits to any specialist physician or physiotherapist
- diagnostic procedures.

Thus, the resulting cost-analysis assessed direct medical costs (Table 21). Direct non-medical costs and indirect costs were not considered.

It is clear that patients who had formerly received CGS spent less on symptomatic drugs, namely analgesics and NSAIDs. In addition, they underwent fewer visits, as well as fewer diagnostic procedures (especially fewer GI endoscopies, most probably because of their lower intake of NSAIDs). When all costs related to such use of health resources were put



Variables	Placebo N=43	CGS N=58
Cost of analgesics - €*	59 (23)	19 (3)
Cost of NSAIDs - €	116 (31)	63 (17)
<b>Total cost of OA† drugs - € (including analgesics, NSAIDs etc) ‡</b>	<b>204 (43)</b>	<b>108 (20)</b>
Number of visits to specialist ‡	2.1 (0.5)	1.8 (0.3)
Number of visits to general practitioner	11.1 (1.5)	9.8 (1.1)
Number of paramedical visits for OA ‡	17.4 (6.3)	6.6 (2.0)
Number of radiographs for OA ‡	0.60 (0.14)	0.44 (0.09)
Number of gastroscopies ‡	0.30 (0.07)	0.10 (0.04)
Number of non-OA exams	5.4 (1.6)	2.8 (0.6)
<b>Total cost calculated for OA-related resources - €</b>	<b>605 (21)</b>	<b>292 (6)§</b>

The data refer to a subset of 101 patients that attended the follow-up clinic visit

\*€ = Euro; OA†=osteoarthritis; ‡Included in total cost calculation; §P=0.024 vs. placebo

**TABLE 21.**

Mean (SE) use of health resources per patient in the year prior to the follow-up evaluation, and total cost calculated for OA-related expenses

together, during the last year of the follow-up period patients formerly on CGS spent less than half of what was spent by patients who had received the placebo.

This cost analysis offers strong evidence of the cost-effectiveness of CGS, even without taking into account the major benefits brought about by the 57% lower risk of undergoing total knee replacement surgery.

## CONCLUSIONS

**CGS 1500 mg once daily is cost-effective for treating OA. CGS compares favorably with both NSAIDs and placebo.**



## CHAPTER 9

### References

1. Felson DT, Lawrence RC, Dieppe PA, et al. *Osteoarthritis: New Insights. Part 1: The Disease and Its Risk Factors*. Ann Intern Med 2000;133:635-646
2. Felson DT and Zhang Y. *An update on the epidemiology of knee and hip osteoarthritis with a view to prevention*. Arthritis Rheum 1998;41:1343-1355
3. O'Reilly S, Doherty M. "Clinical features of osteoarthritis and standard approaches to the diagnosis" In: *Osteoarthritis*. Brandt KD, Doherty M, Lohmander S. (Eds) Oxford Medical Publications. Oxford University Press, Oxford, 1998, pp 197-217
4. Guccione AA, Felson DT, Anderson JJ, et al. *The Effects of Specific Medical Conditions on the Functional Limitations of Elders in the Framingham Study*. Am J Public Health 1994;84:351-358
5. Brandt KD, Lohmander LS, Doherty M. "Introduction: the Concept of Osteoarthritis as Failure of the Diarthrodial Joint" In: *Osteoarthritis*. KD Brandt, M Doherty and LS Lohmander. (Eds) Oxford Medical Publications, Oxford University Press, Oxford, 1998, pp 70-84
6. Bland JH and Cooper SM. *Osteoarthritis: A Review of the Cell Biology Involved and Evidence for Reversibility. Management Rationally Related to Known Genesis and Pathophysiology*. Semin Arthritis Rheum 1984;14:106-133
7. Mankin HJ. *The Reaction of Articular Cartilage to Injury and Osteoarthritis* (first of two parts). N Engl J Med 1974;291:1285-1292
8. Mankin HJ. *The Reaction of Articular Cartilage to Injury and Osteoarthritis* (second of two parts). N Engl J Med 1974;291:1335-1340
9. Fernandes JC, Martel-Pelletier J, Pelletier JP. *The Role of Cytokines in Osteoarthritis Pathophysiology*. Biorheology 2002;39:237-246
10. Blom AB, van der Kraan PM, van den Berg WB. *Cytokine Targeting in Osteoarthritis*. Curr Drug Targets 2007;8:283-292
11. The European Agency for the Evaluation of Medicinal Products. CPMP/EWP/784/97. *Points to Consider on Clinical Investigation of Medicinal Products Used in the Treatment of Osteoarthritis*. July 1998.
12. *Recommendations for the Registration of Drugs Used in the Treatment of Osteoarthritis. Group for the Respect of Ethics and Excellence in Science (GREGS): Osteoarthritis Section*. Ann Rheum Dis 1996;55:552-557

13. Altman R, Brandt KD, Hochberg M, et al. *Design and Conduct of Clinical Trials in Patients with Osteoarthritis: Recommendations from a Task Force of the Osteoarthritis Research Society*. Results from a workshop. *Osteoarthritis Cartilage* 1996;4:217-243
14. Lequesne M, Brandt K, Bellamy N, et al. *Guidelines for Testing Slow Acting Drugs in Osteoarthritis*. *J Rheumatol Suppl* 1994;41:65-71
15. *Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee: 2000 update*. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum* 2000;43:1905-1915
16. Jordan KM, Arden NK, Doherty M, et al. *EULAR Recommendations 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* 2003;62:1145-1155
17. Zhang W, Doherty M, Arden N, et al. *EULAR Evidence Based Recommendations for the Management of Hip Osteoarthritis: Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)*. *Ann Rheum Dis* 2005;64:669-681
18. Towheed TE, Maxwell L, Judd M, et al. *Acetaminophen for Osteoarthritis*. *Cochrane Database Syst Rev* 2006;CD004257
19. Bjordal JM, Ljunggren AE, Klovning A, et al. *Non-Steroidal Anti-Inflammatory Drugs, Including Cyclo-Oxygenase-2 Inhibitors, in Osteoarthritic Knee Pain: Meta-Analysis of Randomised Placebo Controlled Trials*. *BMJ* 2004;329:1317-
20. Zhang W, Moskowitz RW, Nuki G, et al. *OARSI Recommendations for the Management of Hip and Knee Osteoarthritis, Part I: Critical Appraisal of Existing Treatment Guidelines and Systematic Review of Current Research Evidence*. *Osteoarthritis Cartilage* 2007;15:981-1000
21. Zhang W, Moskowitz RW, Nuki G, et al. *OARSI Recommendations for the Management of Hip and Knee Osteoarthritis, Part II: OARSI Evidence-Based, Expert Consensus Guidelines*. *Osteoarthritis Cartilage* 2008;16:137-162
22. Hamerman D. *The Biology of Osteoarthritis*. *N Engl J Med* 1989;320:1322-1330
23. Russell AS, Ghazadeh-Habashi A, Jamali F. *Active Ingredient Consistency of Commercially Available Glucosamine Sulfate Products*. *J Rheumatol* 2002;29:2407-2409
24. Towheed TE and Anastassiades T. *Glucosamine Therapy for Osteoarthritis: An Update*. *J Rheumatol* 2007;34:1787-1790
25. Towheed TE, Maxwell L, Anastassiades TP, et al. *Glucosamine Therapy for Treating Osteoarthritis*. *Cochrane Database Syst Rev* 2005;CD002946-
26. De Wan M and Volpi G. A Method of Preparing Mixed Glucosamine Salts. US patent 5,847,107, 1997
27. Bassleer C, Rovati L, Franchimont P. *Stimulation of Proteoglycan Production by Glucosamine Sulfate in Chondrocytes Isolated from Human Osteoarthritic Articular Cartilage In Vitro*. *Osteoarthritis Cartilage* 1998;6:427-434
28. Noyszewski EA, Wroblewski K, Dodge GR, et al. *Preferential Incorporation of Glucosamine Into the Galactosamine Moieties of Chondroitin Sulfates in Articular Cartilage Explants*. *Arthritis Rheum* 2001;44:1089-1095
29. Vidal Y, Plana RR, Bizzarri D, Rovati AL. *Articular Cartilage Pharmacology. In Vitro Studies on Glucosamine and Non Steroidal Antiinflammatory Drugs*. *Pharmacol Res Commun* 1978;10:557-569
30. Bassleer C, Henrotin Y, Franchimont P. *In-vitro Evaluation of Drugs Proposed as Chondroprotective Agents*. *Int J Tissue React* 1992;14:231-241

31. Piperno M, Reboul P, Hellio Le Graverand MP, et al. *Glucosamine Sulfate Modulates Dys-regulated Activities of Human Osteoarthritic Chondrocytes In Vitro*. *Osteoarthritis Cartilage* 2000;8:207-212
32. Dodge GR, Hawkins DF, Jimenez SA. *Modulation of Aggrecan, MMP1 and MMP3 Production by Glucosamine Sulfate in Cultured Human Articular Chondrocytes*. *Arthritis Rheum* 1999;Suppl. 42:S253
33. Sandy JD, Gamett D, Thompson V, et al. *Chondrocyte-Mediated Catabolism of Aggrecan: Aggrecanase-Dependent Cleavage Induced by Interleukin-1 or Retinoic Acid Can Be Inhibited by Glucosamine*. *Biochem J* 1998;335(Pt 1):59-66
34. Biggee BA, Blinn CM, McAlindon TE, et al. *Low Levels of Human Serum Glucosamine After Ingestion of Glucosamine Sulphate Relative to Capability for Peripheral Effectiveness*. *Ann Rheum Dis* 2006;65:222-226
35. Mroz PJ and Silbert JE. *Use of <sup>3</sup>H-Glucosamine and <sup>35</sup>S-Sulfate With Cultured Human Chondrocytes to Determine the Effect of Glucosamine Concentration on Formation of Chondroitin Sulfate*. *Arthritis Rheum* 2004;50:3574-3579
36. Yaron I, Shirazi I, Judovich R, et al. *Glucosamine Sulfate Inhibits Nitric Oxide and Stromelysin Production in Cartilage Cultures and Reverses IL-1 Inhibition of Osteoarthritic Articular Cartilage Synthesis*. *Ann Rheum Dis* 2001;60 (suppl):50
37. Gouze JN, Bordji K, Gulberti S, et al. *Interleukin-1 $\beta$  Down-regulates the Expression of Glucuronosyltransferase I, a Key Enzyme Priming Glycosaminoglycan Biosynthesis: Influence of Glucosamine on Interleukin-1 $\beta$ -Mediated Effects in Rat Chondrocytes*. *Arthritis Rheum* 2001;44:351-360
38. Shikhman AR, Kuhn K, Alaaeddine N, et al. *N-Acetylglucosamine Prevents IL-1  $\beta$ -Mediated Activation of Human Chondrocytes*. *J Immunol* 2001;166:5155-5160
39. Gouze JN, Bianchi A, Becuwe P, et al. *Glucosamine Modulates IL-1-Induced Activation of Rat Chondrocytes at a Receptor Level, and by Inhibiting the NF $\kappa$  B pathway*. *FEBS Lett* 2002;510:166-170
40. Largo R, Alvarez-Soria MA, Díez-Ortego I, et al. *Glucosamine Inhibits IL-1 $\beta$ -induced NF $\kappa$ B Activation in Human Osteoarthritic Chondrocytes*. *Osteoarthritis Cartilage* 2003;11:290-298
41. Piepoli T, Zanelli T, Letari O, Persiani S, Rovati LC, Caselli G. *Glucosamine Sulfate Inhibits IL-1-Stimulated Gene Expression at Concentrations Found in Humans After Oral Intake*. *Arthritis and Rheumatism* 2005; 52, 9 Suppl: 1326
42. Hoffer LJ, Kaplan LN, Hamadeh MJ, et al. *Sulfate Could Mediate the Therapeutic Effect of Glucosamine Sulfate*. *Metabolism* 2001;50:767-770
43. Uitterlinden EJ, Jahr H, Koevoet JL, et al. *Glucosamine Decreases Expression of Anabolic and Catabolic Genes in Human Osteoarthritic Cartilage Explants*. *Osteoarthritis Cartilage* 2006;14:250-257
44. Conrozier T, Mathieu P, Piperno M, Richard S, Annefeld M, Richard M et al. *Glucosamine Sulfate Significantly Reduced Cartilage Destruction in a Rabbit Model of Osteoarthritis*. *Arthritis Rheum* 1998;41:147
45. Ayral X, Dougados M, Lestrat V, et al. *Arthroscopic Evaluation of Chondropathy in Osteoarthritis of the Knee*. *J Rheumatol* 1996;23:698-706
46. Pelletier JP, Jovanovic D, Lascau-Coman V, Hilal G, Fernandes JC, Martel-Pelletier J. *Relevance of Animal Models to Clinical Disease. Glucosamine Sulfate Reduces the Structural Changes in Dog Experimental Osteoarthritis: Beneficial Effect Through Suppression of the Expression of Collagenase-1*. *Proceedings of a Symposium held at the XIV European League against Rheumatism Congress, Glasgow, June 1999*

47. Chiusaroli R, Natali C, Colombo F, Ballanti P, Rovati LC, Caselli G. *Glucosamine Sulfate Delays Progression of Spontaneous Osteoarthritis in the STR/ort Mouse Model*. Osteoarthritis and Cartilage 2007;15:C227-C228
48. Setnikar I, Giachetti C, Zanolo G. *Absorption, Distribution and Excretion of Radioactivity After a Single Intravenous or Oral Administration of [<sup>14</sup>C] Glucosamine to the Rat*. Pharmatherapeutica 1984;3:538-550
49. Roda A, Sabatini L, Barbieri A, et al. *Development and Validation of a Sensitive HPLC-ESI-MS/MS Method for the Direct Determination of Glucosamine in Human Plasma*. J Chromatogr B Analyt Technol Biomed Life Sci 2006;844:119-126
50. Persiani S, Roda E, Rovati LC, et al. *Glucosamine Oral Bioavailability and Plasma Pharmacokinetics After Increasing Doses of Crystalline Glucosamine Sulfate in Man*. Osteoarthritis Cartilage 2005;13:1041-1049
51. Persiani S, Rotini R, Trisolino G, et al. *Synovial and Plasma Glucosamine Concentrations in Osteoarthritic Patients Following Oral Crystalline Glucosamine Sulphate at Therapeutic Dose*. Osteoarthritis Cartilage 2007;15:764-772
52. Jackson CG, Plaas AH, Barnhill JG, Harris CL, Clegg DO. *The Pharmacokinetics of Oral Glucosamine and Chondroitin Sulfate in Humans*. Arthritis Rheum 2005;52:4062-3 (Abstract L13).
53. Jackson CG, Plaas AH, Barnhill JG, Harris CL, Hua C, Clegg DO. *The Multiple-Dose Pharmacokinetics of Orally Administered Glucosamine and Chondroitin Sulfate in Humans*. Abs 1681/352 presented at the 2006 ACR/ARHP Annual Scientific Meeting, Washington DC.
54. Clegg DO, Reda DJ, Harris CL, et al. *Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis*. N Engl J Med 2006;354:795-808
55. Persiani S, Rovati LC, Pastorini E, Locatelli M, Giacobelli G, Paganini D, Roda A. *Pharmacokinetics of Glucosamine in Man After oral Administration of Crystalline Glucosamine Sulfate or as Glucosamine Hydrochloride Alone or in Combination With Chondroitin Sulfate*. Poster presented at OARSI meeting 2007.
56. Reginster JY, Deroisy R, Rovati LC, et al. *Long-Term Effects of Glucosamine Sulphate on Osteoarthritis Progression: a Randomised, Placebo-Controlled Clinical Trial*. Lancet 2001;357:251-256
57. Pavelka K, Gatterova J, Olejarova M, et al. *Glucosamine Sulfate Use and Delay of Progression of Knee Osteoarthritis: a 3-year, Randomized, Placebo-Controlled, Double-Blind Study*. Arch Intern Med 2002;162:2113-2123
58. Herrero-Beaumont G, Ivorra JA, Del Carmen TM, et al. *Glucosamine Sulfate in the Treatment of Knee Osteoarthritis Symptoms: a Randomized, Double-Blind, Placebo-Controlled Study Using Acetaminophen as a Side Comparator*. Arthritis Rheum 2007;56:555-567
59. Drovanti A, Bignamini AA, Rovati AL. *Therapeutic Activity of Oral Glucosamine Sulfate in OA: a Placebo Controlled Double-Blind Investigation*. Clin Ther 1980;3:260-272
60. Pujalte JM, Llavore EP, Ylescupidéz FR. *Double-Blind Clinical Evaluation of Oral Glucosamine Sulphate in the Basic Treatment of Osteoarthritis*. Curr Med Res Opin 1980;7:110-114
61. Crolle G. and D'este E. *Glucosamine Sulfate for the Management of Arthrosis: a Controlled Clinical Investigation*. Curr Med Res Opin 1980;7:104-109
62. D'Ambrosio E, Casa B., Bompiani R., et al. *Glucosamine Sulfate: a Controlled Clinical Investigation in Arthrosis*. Pharmatherapeutica 1981;2:504-508
63. Noack W, Fischer M, Förster KK, Rovati LC et al. *Glucosamine Sulfate in Osteoarthritis of the Knee*. Osteoarthritis Cartilage 1994;2:51-59

64. Lequesne MG, Mery C, Samson M, et al. *Indexes of Severity for Osteoarthritis of the Hip and Knee. Validation-Value in Comparison With Other Assessment Tests.* Scand J Rheumatol Suppl 1987;65:85-89
65. Förster KK, Schmid K, Rovati LC. *Efficacy of Glucosamine Sulfate in Osteoarthritis of the Lumbar Spine: a Placebo-Controlled, Randomized, Double-Blind Study.* Arthritis Rheum 2000;43 (Suppl):1613
66. Müller-Faßbender H, Bach GL, Haase W, et al. *Glucosamine Sulfate Compared to Ibuprofen in Osteoarthritis of the Knee.* Osteoarthritis Cartilage 1994;2:61-69
67. Qiu GX, Gao SN, Giacovelli G, et al. *Efficacy and Safety of Glucosamine Sulfate versus Ibuprofen in Patients With Knee Osteoarthritis.* Arzneimittelforschung 1998;48:469-474
68. Rovati LC. *The Clinical Profile of Glucosamine Sulfate as a Selective Symptom Modifying Drug in Osteoarthritis: Current Data and Perspectives.* Osteoarthritis Cartilage 1997;5:72
69. Bellamy N, Buchanan WW, Goldsmith CH, et al. *Validation Study of WOMAC: a Health Status Instrument for Measuring Clinically Important Patient Relevant Outcomes to Antirheumatic Drug Therapy in Patients With Osteoarthritis of the Hip or Knee.* J Rheumatol 1988;1988:1833-40
70. Dougados M, LeClaire P, van der Heijde D, et al. *A Report of the Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative.* Osteoarthritis Cartilage 2000;8:395-403
71. Center for Drug Evaluation and Research. *Clinical Development Programs for Drugs, Devices and Biological Products Intended for the Treatment of Osteoarthritis.* Food and Drug Administration (US); July 1999
72. McAlindon T. *Glucosamine for Osteoarthritis: Dawn of a New Era?* Lancet 2001;357:247-248
73. Bruyere O, Compere S, Rovati LC, et al. *Five-year Follow-up of Patients With a Previous 3-year Randomised Controlled Trial of Glucosamine Sulfate in Knee Osteoarthritis.* Arthritis Rheum 2003;48:89-
74. Pavelka K, Gatterova J, Giacovelli G, et al. *Glucosamine Sulfate Prevents Total Joint Replacement in the Long-Term Follow-Up of Knee Osteoarthritis Patients.* Arthritis Rheum 2004;50:251
75. Bruyere O, Pavelka K, Rovati LC, et al. *Total Joint Replacement After Glucosamine Sulphate Treatment in Knee Osteoarthritis: Results of a Mean 8-year Observation of Patients from Two Previous 3-year, Randomised, Placebo-Controlled Trials.* Osteoarthritis Cartilage 2008;16:254-260
76. Bruyere O, Pavelka K, Rovati LC, et al. *Glucosamine Sulfate Reduces Osteoarthritis Progression in Postmenopausal Women with Knee Osteoarthritis: Evidence from Two 3-year Studies.* Menopause 2004;11:138-143
77. Pavelka K, Bruyere O, Rovati LC, et al. *Relief in Mild-To-Moderate Pain Is not a Confounder in Joint Space Narrowing Assessment of Full Extension Knee Radiographs in Recent Osteoarthritis Structure-Modifying Drug Trials.* Osteoarthritis Cartilage 2003;11:730-737
78. Bruyere O, Honore A, Rovati LC, et al. *Radiologic Features Poorly Predict Clinical Outcomes in Knee Osteoarthritis.* Scand J Rheumatol 2002;31:13-16
79. Bruyere O, Honore A, Ethgen O, et al. *Correlation Between Radiographic Severity of Knee Osteoarthritis and Future Disease Progression. Results from a 3-year Prospective, Placebo-Controlled Study Evaluating the Effect of Glucosamine Sulfate.* Osteoarthritis Cartilage 2003;11:1-5
80. Towheed TE, Anastassiades TP, Shea B, et al. *Glucosamine Therapy for Treating Osteoarthritis.* Cochrane Database Syst Rev 2001;CD002946

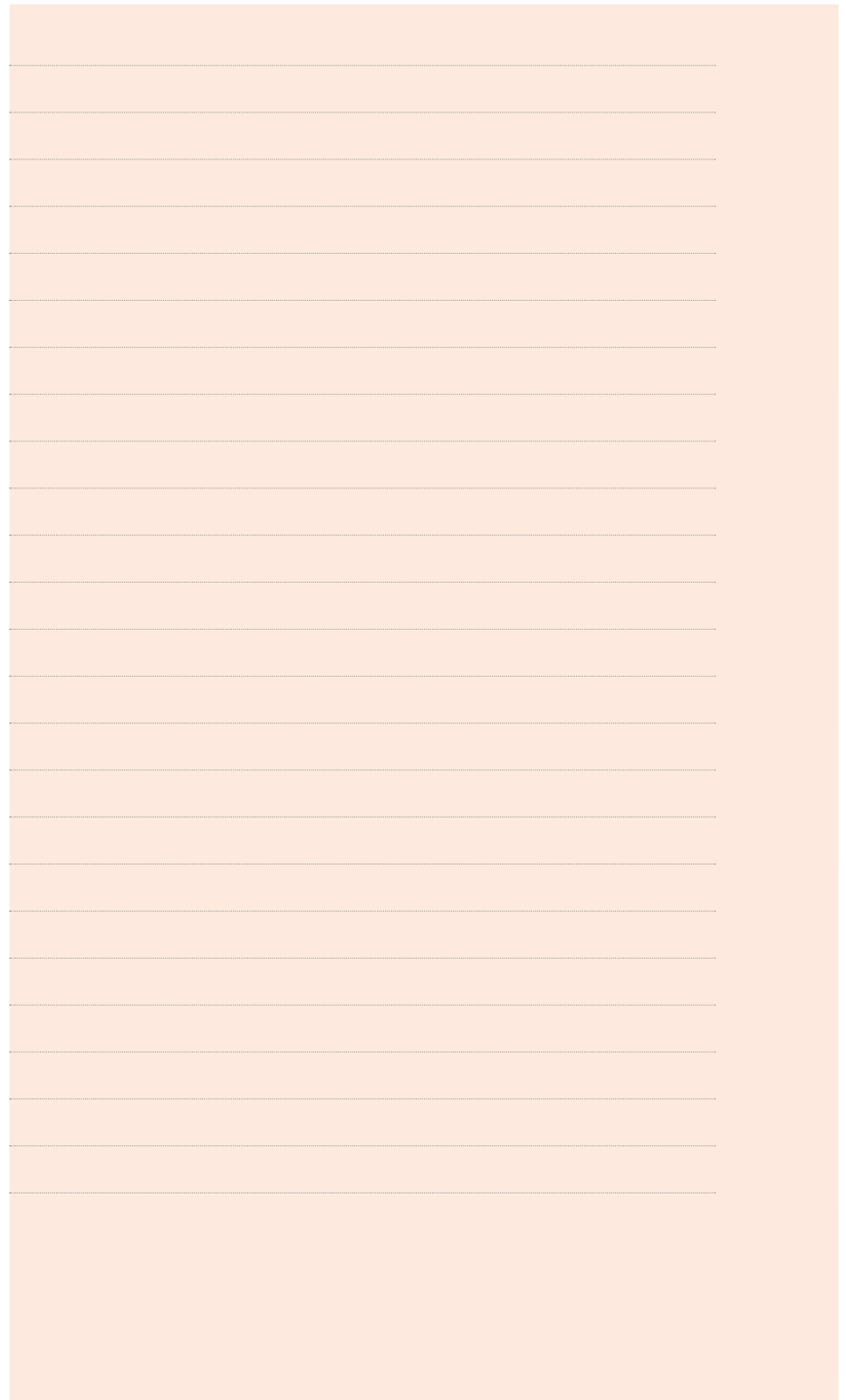
81. Adebowale AO and Cox DS, et al. *Analysis of Glucosamine and Chondroitin Sulfate Content in Marketed Products and the Caco-2 Permeability of Chondroitin Sulfate Raw Materials.* JANA 2000;3:37-44
82. Reginster JY. *The Efficacy of Glucosamine Sulfate in Osteoarthritis: Financial and Non-financial Conflict of Interest.* Arthritis Rheum 2007;56:2105-2110
83. Cibere J, Kopec JA, Thorne A, et al. *Randomized, Double-Blind, Placebo-Controlled Glucosamine Discontinuation Trial in Knee Osteoarthritis.* Arthritis Rheum 2004;51:738-745
84. Hughes R and Carr A. *A randomized, Double-Blind, Placebo-Controlled Trial of Glucosamine Sulphate as an Analgesic in Osteoarthritis of the Knee.* Rheumatology (Oxford) 2002;41:279-284
85. Hout JB, McMillan R, Wein C, et al. *Effect of Glucosamine Hydrochloride in the Treatment of Pain of Osteoarthritis of the Knee.* J Rheumatol 1999;26:2423-2430
86. Sawitzke AD, Shi H, Finco MF, et al. *The Effect of Glucosamine and/or Chondroitin Sulfate on the Progression of Knee Osteoarthritis: a Report from the Glucosamine/Chondroitin Arthritis Intervention Trial.* Arthritis Rheum 2008;58:3183-3191
87. Hochberg MC. *Nutritional Supplements for Knee Osteoarthritis - Still No Resolution.* N Engl J Med 2006;354:858-860
88. Conte A., Volpi N, Palmieri L, et al. *Biochemical and Pharmacokinetic Aspects of Oral Treatment With Chondroitin Sulfate.* Arzneimittelforschung 1995;45:918-925
89. Karzel K and Domenjot R. *Effects of Hexosamine Derivatives and Uronic Acid Derivates on Glycosaminoglycan Metabolism of Fibroblast Cultures.* Pharmacology 1971;337-345
90. Herrero-Beaumont G, Rovati LC. *Use of Crystalline Glucosamine Sulfate in Osteoarthritis.* Future Rheumatol 2006;1(4):397-414
91. Baron AD, Zhu JS, Zhu JH, et al. *Glucosamine Induces Insulin Resistance In Vivo by Affecting GLUT 4 Translocation in Skeletal Muscle.* J Clin Invest 1995;96:2792-2801
92. Shankar RR, Zhu JS, Baron AD. *Glucosamine Infusion in Rats Mimics the  $\beta$ -cell Dysfunction of Non-Insulin-Dependent Diabetes Mellitus.* Metabolism 1998;47:573-577
93. McNamara PS, Barr SC, Erb HN. *Hematologic, Hemostatic, and Biochemical Effects in Dogs Receiving an Oral Chondroprotective Agent for Thirty Days.* Am J Vet Res 1996;57:1390-94
94. Echard BW, Talpur NA, Funk KA, et al. *Effects of Oral Glucosamine and Chondroitin Sulfate Alone and in Combination on the Metabolism of SHR and SD Rats.* Mol Cell Biochem 2001;225:85-91
95. Monauni T, Zenti MG, Cretti A, et al. *Effects of Glucosamine Infusion on Insulin Secretion and Insulin Action in Humans.* Diabetes 2000;49:926-935
96. Pouwels MJ, Jacobs JR, Span PN, et al. *Short-Term Glucosamine Infusion Does Not Affect Insulin Sensitivity in Humans.* J Clin Endocrinol Metab 2001;86:2099-2103
97. Tannis AJ, Barban J, Conquer JA. *Effect of Glucosamine Supplementation on Fasting and Non-Fasting Plasma Glucose and Serum Insulin Concentrations in Healthy Individuals.* Osteoarthritis Cartilage 2004;12:506-511
98. Scroggie DA, Albright A, Harris MD. *The Effect of Glucosamine-Chondroitin Supplementation on Glycosylated Hemoglobin Levels in Patients With Type 2 Diabetes Mellitus: a Placebo-Controlled, Double-Blinded, Randomized Clinical Trial.* Arch Intern Med 2003;163:1587-1590
99. Rovati LC, Annesfeld M, Giacovelli G, et al. *Glucosamine in Osteoarthritis.* Lancet 1999;354:1640-1642



100. Anderson JW, Nicolosi RJ, Borzelleca JF. *Glucosamine Effects in Humans: a Review of Effects on Glucose Metabolism, Side Effects, Safety Considerations and Efficacy*. Food Chem Toxicol 2005;43:187-201
101. Stumpf JL and Lin SW. *Effect of Glucosamine on Glucose Control*. Ann Pharmacother 2006;40:694-698
102. Bailey CJ and Turner SL. *Glucosamine-Induced Insulin Resistance in L6 muscle cells*. Diabetes Obes Metab 2004;6:293-298
103. Gray HC, Hutcheson PS, Slavin RG. *Is Glucosamine Safe in Patients With Seafood Allergy?* J Allergy Clin Immunol 2004;114:459-460
104. Garrote Garcia M et al. *Interacción farmacológica del sulfato de glucosamina con acenocumarol*. Atención Primaria 2004; 33(3):162-4
105. Rozenfeld V, Crain JL, Callahan AK. *Possible Augmentation of Warfarin Effect by Glucosamine-Chondroitin*. Am J Health Syst Pharm 2004;61:306-307
106. Potter JL. *Glucosamine and Warfarin Interaction*. The Pharmaceutical Journal 2006; 277:247
107. Knudsen JF and Sokol GH. *Potential Glucosamine-Warfarin Interaction Resulting in Increased International Normalized Ratio: Case Report and Review of the Literature and MedWatch Database*. Pharmacotherapy 2008;28:540-548
108. Mantovani LG, Belisari A, Cristoforetti C, Giacovelli G and Rovati LC. *Cost-Benefit Analysis of Glucosamine Sulfate Use*. Ann Rheum Dis 2001;60 (Suppl 1):236



## NOTES



A large, light orange rectangular area containing horizontal dotted lines for writing notes. The area is designed for taking notes and occupies the majority of the page below the header.



## NOTES



## NOTES

A large, light orange rectangular area with horizontal dotted lines, intended for taking notes. The area is bounded by a solid orange border on the top, bottom, and right sides, and a solid orange border on the left side. The interior of the rectangle is filled with light orange and contains 20 horizontal dotted lines for writing.

