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Glucosamine Hydrochloride (Alateris®)

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

- Glucosamine is a constituent of glycosaminoglycans in cartilage and synovial fluid. It has been available as a food supplement for many years.
- One brand of glucosamine hydrochloride (Alateris®) has recently been licensed in the UK for relief of symptoms in mild-moderate osteoarthritis (OA) of the knee.
- A Cochrane review of glucosamine in osteoarthritis concluded that the eight randomised controlled trials that had adequate concealment of treatment demonstrated a small non-significant benefit of glucosamine over placebo for pain relief in knee OA (standardised mean difference (SMD) -0.19, 95% confidence interval (CI) -0.50 to 0.11). Results for joint function were conflicting – Lequesne Index scores from 3 trials demonstrated a moderate difference, (SMD -0.61 (95% CI -1.21 to -0.01, n=599). Five other trials that used WOMAC scoring found a very small difference between glucosamine and placebo (WOMAC total score SMD -0.15 (-0.30 to 0.00, n=672) and WOMAC function subscale SMD -0.07 (-0.21 to 0.08, n=750).
- The licensed dose of glucosamine hydrochloride (Alateris®), delivers a similar amount of glucosamine as 1500mg glucosamine sulphate, the dose and salt most commonly used in trials. Existing published trial data involving both sulphate and hydrochloride salts of glucosamine has been used to support licensing of this product, no new trials have been carried out.
- Recent NICE guidance on osteoarthritis (February 2008) does not recommend use of glucosamine.[1]

Brand Name, (Manufacturer): Alateris® (William Ransom & Son PLC)

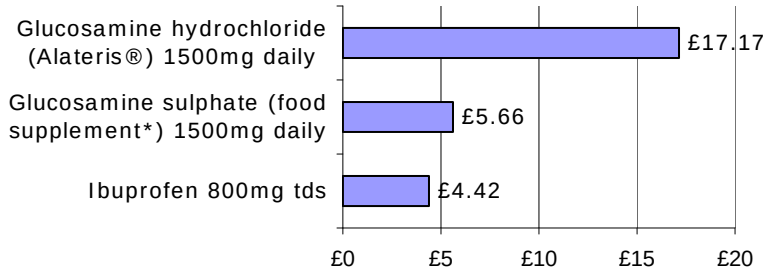
BNF Therapeutic Class: Other drugs for rheumatic diseases

Licensed Indications: Relief of symptoms in mild to moderate osteoarthritis of the knee, not indicated for acute painful symptoms

Dosage and Administration: Two tablets daily. Each tablet contains glucosamine hydrochloride 750mg, equivalent to 625mg of glucosamine base.

Marketed: October 2007

Cost Comparisons: Cost for 28 days treatment*: (prices from MIMS, Drug Tariff, March 2008; glucosamine price based on PPA data 2007)*



* Typical price when prescribed, based on top 5 products dispensed, PPA data 2007. Retail prices vary widely.

N.B. Doses shown for general comparison and do not imply therapeutic equivalence.

Introduction

Osteoarthritis (OA) is a common condition and prevalence increases with advancing age. Around 10% of people over 55 are thought to have substantial disability due to OA of the knee. Hip and hand joints are also commonly affected. The mainstay of treatment is symptom management with analgesics such as paracetamol and non steroidal anti-inflammatory drugs (NSAIDs).[1] Interest in other therapies such as glucosamine has increased in recent years.

Evidence

Data from a Cochrane review[2] of 20 trials of glucosamine in OA is summarised in Table 1 (see Appendix). Although analysis of data from eight trials with adequate concealment found no benefit of glucosamine over placebo, data from 15 trials included in the pooled analysis found a 28% improvement in pain score and a 21% improvement in joint function using the Lequesne Index. Results from these trials using WOMAC scores (Western Ontario and McMasters University osteoarthritis index) for pain, function and stiffness did not find a statistically significant difference between glucosamine and placebo. It is not clear why there was a difference between results using the two scoring systems for joint function.

One brand of glucosamine sulphate that is not widely available in the UK was used in 10 of the 20 trials (Rotta, Italy). This brand was used in two studies of three years duration, which reported significantly less narrowing of the knee joint space with glucosamine than with placebo.[3,4] However fewer than two thirds of trial participants completed the studies and the conclusion that glucosamine has disease-modifying properties has not been confirmed. A recent placebo controlled randomised trial of another brand of glucosamine in patients with hip OA failed to demonstrate any benefit in pain or joint narrowing after two years' treatment.[5]

Another systematic review of trials comparing glucosamine with placebo found significantly greater heterogeneity among the trials, more than would be expected by chance.[6] The effect size of glucosamine was found to be very small where there was no sponsorship of trials but was much larger where there was industry involvement (effect sizes of 0.06 and 0.44, respectively (see Table 1, Appendix).

A further randomised controlled trial investigated discontinuation of glucosamine treatment in 137 patients who had previously experienced at least moderate improvement in symptoms while taking it for at least a month. They were randomised to continue with either placebo or glucosamine sulphate 1500mg daily. After 6 months, there was no significant difference in the proportion of patients in either group who experienced disease flare (42% vs. 45% respectively p=0.76), demonstrating a lack of symptomatic benefit from continued use of glucosamine.[7]

Thirteen trials were submitted to the EMEA for the European licensing of glucosamine hydrochloride (Alateris®), all were in the Cochrane review.[3,4,8-18] None of the trials involved the use of this product.

Five of the trials in the licence application were found by the Cochrane reviewers to have inadequately concealed treatment allocation.

Nine trials compared glucosamine with placebo. Two of these were the three-year trials measuring joint space narrowing, referred to above where there was a large dropout rate.[3,4]

One of the nine trials comparing glucosamine and placebo was in patients with an average age of 41-43 experiencing 'regular knee pain', not necessarily osteoarthritis[7] (and was excluded from the Cochrane analysis). The remaining six trials[8-13] involved relatively short-term treatment (1-2 months in four, one of 12 weeks and one of 6 months duration). The trial that lasted 6 months (n=80) found no difference between glucosamine and placebo in pain score, WOMAC score or pain questionnaire. A small difference in knee flexion was detected but this could have been due to measurement error.[14]

The remaining four trials submitted for the licence compared glucosamine with a NSAID (ibuprofen), in patients with OA.[15-18] One of these involved patients with temperomandibular arthritis and was excluded from analysis in the Cochrane review;[15] two others were found to have inadequate concealment of treatment[16,17]. The remaining randomised controlled trial[18] lasted four weeks and involved 200 hospitalised patients with active knee OA, and a mean Lequesne index score for joint function of about 16. A successful treatment, that is, a reduction in Lequesne index score of at least 2 points (if initial score was over 12 points), or a reduction in 1 point (if initial score was less than 12 points), was found in similar proportions in the ibuprofen and glucosamine groups (52% and 48% respectively). Ibuprofen produced improvement in symptoms sooner than glucosamine, but there was no difference between the two from the second week onward. The lack of a placebo group in this trial makes it difficult to quantify the magnitude of the benefit of either of the treatments (particularly since the 1200mg/day dose of ibuprofen used was probably suboptimal). In all four trials more patients taking NSAIDs than glucosamine experienced adverse effects, mainly gastro-intestinal and withdrew from treatment (7% vs. 1% respectively in the trial described above).[18]

Tables 2 and 3 (Appendix) summarise results from the trials in the licence submission.

More recently, a large government-funded multicentre randomised controlled trial in the USA compared glucosamine hydrochloride, chondroitin or the two combined, with placebo and celecoxib.[18] This lasted 24 weeks and involved 1583 patients with painful knee osteoarthritis. The primary outcome measure was the number of patients with a 20% decrease in knee pain from baseline until the end of the trial. There was no significant difference between those taking glucosamine alone, glucosamine plus chondroitin or placebo (primary outcome 64%, 66.6% and 60.1% respectively, p=0.30 and p=0.09). A subgroup of patients with moderate-severe OA had a higher response rate, but the numbers of patients were small (and this is outside the licensed indication for Alateris®).

Safety

Glucosamine has not been studied systematically for adverse effects and interactions, unlike other newly licensed products. Adverse effects include nausea, abdominal pain, indigestion, constipation, diarrhoea. Headache, tiredness, rash, itching and flushing are less common.

Other possible effects include a worsening of glucose tolerance, raised lipid levels and possible exacerbation of asthma.[1] Taking glucosamine concurrently with warfarin has been reported to increase INR.

There is no data on those with impaired renal or hepatic function, and the manufacturer has no information on dose modification in such patients.[1]

Appendix: Tables of Clinical trials

Risk Management Issues:

Glucosamine sulphate (food supplement) is unlicensed and the quality of the product is not regulated by the MHRA.

People who are allergic to shellfish should not take some glucosamine preparations including Alateris®, as this is the source of the product.

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Key papers are highlighted in **bold**

Appendix

Table 1: Systematic reviews

	Studies reviewed	Trials analysed	Effect size (95% Confidence interval)	Comment
2	Cochrane review, 2005. Randomised controlled trials assessing effectiveness of glucosamine compared with placebo in osteoarthritis. One trial out of 15 used glucosamine hydrochloride, all others glucosamine sulphate.	Eight trials with adequate concealment of treatment allocation in knee OA	Standardised mean difference (SMD) pain: -0.19 (-0.50 to 0.11), n= 1111 (8 trials) Function (Lequesne index) SMD: -0.61 (-1.21 to -0.01), n =599 (3 trials) WOMAC total score SMD: -0.15 (-0.30 to 0.00), n= 672 (5 trials) WOMAC function subscale SMD:-0.07 (-0.21 to 0.08), n = 750 *Note: Negative SMD indicates glucosamine superior to placebo. Effect size of 0.2 is classed as small, effect size of 0.5 described as moderate.*	Not significant (NS) Results significant NS NS
		All 15 trials	Pain SMD: -0.61 (-0.95 to -0.28); 15 trials, n = 1481	Results significant
		Rotta preparations 10 trials	Pain: SMD -1.31 (-1.99 to -0.64); 7 trials, n = 730 Function (Lequesne index): SMD -0.51 (-0.96 to -0.05); 4 trials, n = 741	Results significant Results significant
		Non-Rotta preparations 8 trials	Pain (WOMAC): SMD -0.15 (-0.35 to 0.05); 8 trials, n = 751 WOMAC total score: SMD -0.02 (-0.27 to 0.22); 3 trials n=258 Function (WOMAC) SMD 0.03 (-0.18 to 0.25); 4 trials, n = 336	NS NS NS
	Randomised controlled trials comparing GS* with NSAIDs in knee osteoarthritis	4 trials (2 Rotta)	Pain: SMD -0.40 (-0.60 to 0.19); 3 trials, n=362 Lequesne index: SMD -0.36 (-1.07 to 0.35); 2 trials, n=345 *Negative value indicates glucosamine superior.*	Result significant NS
	Safety compared with placebo	17 studies	RR 0.97 (0.88 to 1.08) for reported adverse events, RR 0.82 (0.56 to1.21) for withdrawal from trial	NS
6	Randomised double blind placebo controlled trials of glucosamine for pain from osteoarthritis of knee or hip.	All 15 trials	Overall: Summary effect size 0.35 (0.14 to0.56). I^2 = 0.80 (substantial heterogeneity)	
		Industry involvement (11 trials) No industry involvement (4 trials)	Summary effect size 0.47 (0.24 to 0.70), I^2 = 0.81 Summary effect size 0.05 (-0.32 to 0.41), I^2 =0.00	Substantial heterogeneity No heterogeneity
		Rottapharm products (8 trials)	Summary effect size 0.55 (0.29 to 0.82), I^2 =0.84	Substantial heterogeneity
		Non-Rotta preparations (7 trials)	0.11 (-0.16 to 0.38), I^2 =0.00	No heterogeneity
		Trials with adequate concealment (5)	Summary effect size 0.09 (-0.24 to 0.42), I^2 =0.00	No heterogeneity

*GS: glucosamine sulphate

Table 2: Glucosamine compared with placebo - studies submitted to EMEA for licensing of Alateris®

Ref no	Trial design	Trial population	GS* dose Brand	Primary outcome	Comment
3	Randomised double blind (DB) placebo comparison 3 years	212 patients with osteoarthritis (OA) of the knee	1500mg Rotta	Mean joint space change in glucosamine group after 3 years, -0.06mm (-0.22 to 0.09), placebo -0.31 mm (-0.48 to -0.13, p=0.043; total WOMAC score -11.7% (-20.3 to -3.2%); +9.8% (-6.2 to 25.8%), p=0.02 respectively	ITT analysis 36% of glucosamine group and 33% placebo group did not complete trial. 51% of participants were not on treatment for OA during 6 months prior to trial
4	Randomised DB placebo comparison 3 years	202 patients with OA knee	1500mg Rotta	Mean joint space change in glucosamine group at 3 years, 0.04mm (-0.06 to 0.14); placebo -0.19 (-0.29 to -0.09), p=0.01. Mean Lequesne score change after 3 years, -1.7 (-2.2 to -1.2) for glucosamine, -0.82 (-1.1 to -0.51) placebo, p=0.02.	ITT analysis. 35% of glucosamine group and 46% placebo group did not complete trial. No difference between groups in analgesic (paracetamol) use as 'rescue'.
8	Randomised DB placebo comparison 12 weeks	46 patients with OA and/or knee injury	2000mg	Increased walking distance and reduced knee pain with glucosamine vs. placebo	Excluded from Cochrane analysis: diagnosis 'regular knee pain' not necessarily OA, included some with cartilage injury. Average age 41-43. Groups not matched for duration of knee pain.
9	Randomised DB placebo comparison 30 days	80 patients with OA multiple sites	1500mg Rotta	Significant reductions (glucosamine vs. placebo) in: articular pain (69.2% vs. 41.3%), joint tenderness (75.4% vs. 43.6%), swelling (77.1% vs. 44.9%), restriction of active and passive movement (all statistically significant p<0.001)	Generalised, cervical lumbosacral and 'other' OA Cochrane review – inadequate concealment of treatment
10	Randomised DB placebo comparison 6-8 weeks	24 patients with OA knee	1500mg Rotta	Significant reductions (glucosamine vs. placebo) in scores for articular pain (45.7% to 9.2%), joint tenderness (45% to 13.3%), swelling (43.2% to 12.5%), all p<0.01.	Cochrane review – inadequate concealment of treatment Four patients (16.7%) did not complete the trial
11	Randomised DB placebo comparison 4 weeks	252 patients with OA knee	1500mg Rotta	Significant reduction in Lequesne score (greater mean fall with glucosamine compared with placebo (3.2 points vs. 2.2, p<0.05). Number of responders: 55% glucosamine, 38% placebo (52% and 37% respectively on ITT analysis).	
12	Randomised DB placebo comparison 8 weeks	118 patients with OA knee	1500mg Not GS see comment	Mean WOMAC pain score fell from baseline of 42-46 by 9.74 glucosamine group, 3.86 placebo, p = 0.10, NS. No significant changes in WOMAC stiffness or function scores.	Study used Glucosamine hydrochloride 101 patients started treatment at week 0 and 98 completed 8 weeks trial.

13	Randomised DB placebo comparison 2 months (60 days)	114 patients with OA knee	1500mg Non-Rotta	Mean changes from baseline in ten point visual analogue pain score: at rest, glucosamine vs. placebo, 0.73±2.7 vs. 0.59±2.9, p=0.81. For walking, mean change from baseline 1.4±3.0 (SD) and 1.5 ±2.5 respectively, p = 0.77	Cochrane review – inadequate concealment of treatment Trial involved men only Per protocol analysis; 114 recruited. 10 lost to follow up, 6 withdrew. Data analysis on remaining 98.
14	Randomised DB placebo comparison 6 months	80 patients with OA knee	1500mg Non-Rotta	Pain measured using 100 point VAS global pain score. Area under curve analysis found no difference between glucosamine and placebo (mean difference 0.15mm (-8.78 to 9.07). Placebo response in 33%.	A difference of 20mm is recognised as clinically significant in comparing treatments using 100 point VAS scale. Small but significant improvement in knee flexion found with glucosamine compared with placebo, 13º (-23.13, -1.97), could have been due to measurement error.

*GS: glucosamine sulphate

Table 3: Glucosamine compared with Non-steroidal anti-inflammatory drugs (NSAIDs) - studies submitted to EMEA for licensing of Alateris

Ref no	Trial design	Patients	GS* dose Brand	Primary outcome	Comment
15	Randomised double blind comparison with ibuprofen 400mg tds (no placebo group). 3 months (90 days)	45 patients Non knee OA	1500mg Non-Rotta	Number of patients reaching 20% reduction in pain score: (71% glucosamine, 61% ibuprofen, p=0.73, non-significant (NS).	Excluded from Cochrane analysis – temperomandibular OA. Six patients from original 45 did not complete trial
16	Randomised double blind comparison with ibuprofen 1200mg daily for 4 weeks	178 patients with OA knee	1500mg Rotta	No significant difference between groups (knee pain at rest, movement, knee swelling). Sum of scores: -4.82 for glucosamine, -4.28 ibuprofen; both significant reduction from baseline, NS between groups.	Cochrane review – inadequate concealment of treatment
17	Randomised double blind comparison with ibuprofen 400mg tds 8 weeks	40 patients with OA knee	1500mg Unknown brand	Pain scored on scale 1-3. Mean pain score for glucosamine group initially 2.2±0.4, fell to 0.8±0.5 after 8 weeks; ibuprofen from 2.3 ±0.6 to 1.2±0.6; glucosamine superior, p<0.05.	Cochrane review – inadequate concealment of treatment. Analysis based on 38 that completed trial.
18	Randomised double blind comparison with ibuprofen 400mg tds 4 weeks	200 patients with OA knee	1500mg Rotta	Proportion that responded to treatment by reduction in Lequesne index compared with baseline (see text): 52% of ibuprofen group, 48% of glucosamine group; p=0.67.	

*GS: glucosamine sulphate