PrescQIPP Community Interest Company

Glucosamine

This is one of a number of bulletins providing further information on medicines that should be given a low priority, are poor value for money, suitable for self care or for which there are safer more suitable alternatives. This guidance will support Clinical Commissioning Groups (CCGs) in taking action on items that should not routinely be prescribed in primary care or on the NHS.

Further bulletins, including the overarching low value medicines bulletin are available on the PrescQIPP website, available at https://www.prescqipp.info/drop-list/headline-areas/the-prescqipp-drop-list#low-value-medicines-lvm

Glucosamine, in its unlicensed form as a food supplement, has been commonly used for many years for the relief of pain and symptoms associated with joint disorders. Glucosamine, available as glucosamine sulphate or glucosamine hydrochloride, is indicated for the relief of symptoms in mild to moderate osteoarthritis of the knee. However, despite its extensive use and now licensed indications, a number of evidence based systematic literature reviews have not found it to be cost effective.

Recommendations

- Glucosamine (with or without chondroitin) is not recommended for prescribing on the NHS as the evidence to support its efficacy is not strong enough and it is not considered to be cost-effective.
- Patients already being prescribed glucosamine should be reviewed and prescriptions stopped. No new prescriptions of glucosamine containing products should be commenced.
- Patients wishing to take glucosamine should be advised to purchase it over-the-counter.

Background

Osteoarthritis (OA) is the most common chronic joint condition in individuals aged over 65 years and refers to a clinical syndrome of joint pain associated with varying degrees of functional immobility and reduced quality of life.[1] It is estimated that around 10 million people in the UK have a form of arthritis.[2] Projections suggest that this figure is set to increase by 50% by 2030.[2] The most common site of peripheral joint pain lasting for more than one week in the past month, in adults 45 years old and over, is in the knee (19%) and the highest prevalence of knee pain is among women aged 75 years and over (35%).[3] Osteoarthritis has a considerable impact on health services and is the most common form of arthritis, and one of the leading causes of pain and disability worldwide.[4]

Clinical evidence

Glucosamine has historically been used as a dietary supplement for maintaining the elasticity, strength and resilience of cartilage in joints, and is claimed to help reduce joint damage. This has led to the widespread administration of glucosamine with the intent to stimulate production of cartilage components and to allow rebuilding of damaged cartilage.[5]

NICE updated its clinical guidance on the management of OA in February 2014 and their “do not do’ recommendation on the use of glucosamine remains unchanged.[4] Their overall recommendations are:[4]

- Exercise should be a core treatment for people with osteoarthritis, irrespective of age, co-morbidity, pain severity or disability.

- Interventions to achieve weight loss should be a core treatment for people with OA who are obese or overweight.
- Prescribers should consider offering paracetamol for pain relief in addition to core treatment; regular dosing may be required. Paracetamol and/or topical NSAIDs should be considered ahead of oral NSAIDs, cyclo- oxygenase 2 (COX-2) inhibitors or opioids. Please note: NICE will be reviewing CG177 as their surveillance suggests that paracetamol may not have a clinically important effect on pain in people with osteoarthritis.[4]
- When a person presents with osteoarthritis, do not prescribe rubefacients, intra-articular hyaluronan injections, acupuncture, chondroitin or glucosamine products.

NICE highlighted that the available evidence for glucosamine is not strong enough to warrant recommending that it should be prescribed on the NHS.[4] Randomised, placebo-controlled trials of adequate power and duration (related to the structural end point under consideration) should be undertaken to determine the benefits and side effects of agents with disease-modifying osteoarthritis drug potential for treating both hip and knee osteoarthritis (separately).[4]

The evidence NICE used for glucosamine in their original 2008 guidance (which remains unchanged in the 2014 update) was a Cochrane review written in 2005.[6] The review of the clinical trials of glucosamine in knee osteoarthritis published in 2005 was updated in 2008 and did not find a consistent benefit of glucosamine in pain, joint function or stiffness. The review looked at 25 randomised controlled trials representing a total of 4,963 patients using glucosamine hydrochloride or glucosamine sulphate. The review did find that several trials using an Italian brand of glucosamine sulphate (now marketed in the UK as Glusartel®) which were sponsored by the manufacturer, provided a greater improvement in symptoms than placebo.[6]

There have been a number of evidence based, systematic literature reviews undertaken[7-10] and evaluated appraisals written,[11-12] which examine the use of glucosamine for relieving the symptoms in patients with mild to moderate OA of the knee. The recommendations from this clinical evidence are summarised below.

An article in Arthritis Research & Therapy in January 2012 summarises the current evidence base for glucosamine.[13] The symptomatic effect size of glucosamine varies greatly depending on the formulation used and the quality of the clinical trials. The effect size reduces when evidence is accumulated chronologically and evidence for the structure-modifying effects of glucosamine are sparse. The majority of published clinical trials reported a significant ratio of subjects who failed to respond to treatment so the question of benefit remains largely unanswered. Glucosamine is generally safe and no major adverse events have been reported so far, although the glucosamine sulphate sodium chloride preparations are high in sodium and provide up to 30% of the daily recommended maximum intake of salt. The lack of reported adverse events in clinical trials could be attributable to the short duration of patient exposure to treatment.

The European Food Safety Authority has previously reviewed several health claims relating to glucosamine alone or in combination with chondroitin sulphate for reduction of inflammation, maintenance of joints, reduced rate of cartilage degeneration and reduced risk of development of OA.[14] On every occasion, the scientific opinion of the Panel on Dietetic Products, Nutrition and Allergies was that a cause and effect relationship could not be established.

A systematic review and network meta-analysis published in the British Medical Journal reviewed ten trials and looked at the effects of glucosamine, chondroitin, or placebo on pain intensity and change in minimal width of joint space in 3,803 patients with OA of the hip or knee.[7] Glucosamine sulphate 800mg to 1500mg daily was used in eight of the trials. The authors concluded that compared with placebo, none of these drugs or their combinations have any impact on either reducing joint pain or narrowing of joint space. Estimated differences between glucosamine, chondroitin and placebo were less pronounced in seven trials which were industry independent compared to three industry sponsored

trials. Estimated treatment effects in industry independent trials were small or absent and clinically irrelevant.

A Health Technology Assessment assessed the clinical and cost effectiveness of glucosamine sulphate/hydrochloride and chondroitin sulphate in modifying the progression of OA of the knee, and reviewed a total of five systematic reviews and one clinical guideline.[8] The authors concluded that there was evidence that glucosamine sulphate showed some limited clinical effectiveness in the treatment of OA of the knee. No trial data came from the UK and caution is needed in generalising the findings to the UK health-care setting. Cost effectiveness was not conclusively demonstrated, but substantial uncertainty was observed for some key determinants in the model.

One review looked at why trials involving glucosamine often reported a range of estimates for clinical efficacy, hence making it more difficult to draw any conclusions.[9] Fifteen suitable trials were identified, which represented 2,613 patients treated with glucosamine for OA of the knee. Thirteen trials used glucosamine sulphate and three trials used glucosamine hydrochloride. They concluded that heterogeneity among trials of glucosamine was larger than would be expected by chance. Glucosamine hydrochloride was deemed to be not effective. Glucosamine sulphate was deemed to have a moderate effect size but heterogeneity was marked, suggesting that differences between the studies are large and that pooling results is inadvisable. Among the 11 trials with industry involvement, effect sizes were consistently higher. Potential explanations include different glucosamine preparations, inadequate allocation concealment, and industry bias.

Dietary changes (as well as exercise/physical activity) are effective in the treatment of OA, primarily in the knee.[15,16] Research into the causes of OA and its progression have also shown that a reduction in body fat can give greater symptomatic relief that can be explained by the reduction in body weight alone.[17]

Glusartel®, Dolenio®, Yointy®, Alateris® and generics

The marketing authorisations for the licensed products were granted on bibliographic applications.[10,18,19] The data submitted in the application for Glusartel® is based on the extensive clinical experience with glucosamine sulphate. The Glusartel® UKPAR[18] cites two trials[20,21] in the efficacy section published in 1994 and 2001 which have been reviewed in the Cochrane and MTRAC reviews and Wandel et al and Vlad et al papers.[7-9,11]

The Drug and Therapeutics Bulletin (DTB) reviewed the evidence for glucosamine in knee osteoarthritis in 2008 and focused on Alateris® (glucosamine hydrochloride). The reviewers concluded that Alateris® should not be prescribed on the NHS as there is no direct clinical trial evidence of the efficacy and safety of the specific product as it was licensed based on bibliographic data on use of glucosamine in OA. Published evidence suggests glucosamine sulphate (1500mg daily) provides modest pain relief and is relatively safe, however, questions about the cost effectiveness of glucosamine sulphate make it difficult to advise prescribing it on the NHS. However, if patients wanted to, they could purchase their own glucosamine supplies.[10]

MTRAC also reviewed Alateris® (glucosamine hydrochloride) in 2008 and summarised the results of 17 published, double blind, randomised controlled trials of glucosamine of which at least 11 used glucosamine sulphate. MTRAC concluded that glucosamine products (either salt) are not considered suitable for prescribing and that current clinical evidence for its efficacy is inconsistent and not convincing, despite the many trials available. Where any benefits of glucosamine were identified, they were small and clinically insignificant.[11]

The Scottish Medicines Consortium (SMC) does not recommend use of Glusartel® within NHS Scotland as the manufacturer did not present a sufficiently robust clinical and economic analysis to gain acceptance.[12] The manufacturer had specifically requested the SMC to consider the use of Glusartel® in OA patients who would otherwise not be able to take paracetamol or an NSAID (due to inadequate efficacy, liver function abnormalities, gastrointestinal and cardiovascular risk or the need for long term

treatment). However, the manufacturer was unable to provide sufficient evidence to the SMC in this specific patient group. The SMC were also concerned with a number of other factors, such as:

- The doses of paracetamol used in the comparative studies (maximum 3g/day) were not the same as those used in the UK (maximum 4g/day)
- The trial data results could not be generalised to the Scottish OA patient population
- The glucosamine effect size quoted in the trials were small and hence considered to be clinically uncertain
- Recruitment of patients to specific studies may not be representative of the Scottish population.

The SMC was not able to recommend use of Dolenio® for symptomatic treatment of mild to moderate OA of the knee, as the holder of the marketing authorisation has not made a submission to the SMC.[22]

Patients wishing to take glucosamine-containing products (or chondroitin) should be advised to purchase it over the counter. However, please note that the MHRA has warned against glucosamine use by people who have seafood allergies or those taking warfarin.[23]

Costs

The table below shows the annual cost of glucosamine compared to other medicines used for OA in primary care. The prices are from the July 2017 Drug Tariff.[24]

Drug	Dose regimen	Drug cost per year (£)
Glucosamine sulphate 1.5mg tablets (Dolenio®)	1500mg orally once daily	£221
Glucosamine hydrochloride 625mg tablets (Alateris®)	1250mg orally once daily	£224
Paracetamol	1g orally up to four times daily	up to £62
Naproxen	250mg to 500mg twice daily	£24 to £33
Ibuprofen	400mg to 600mg orally three times daily	£41 to £82
Celecoxib	200mg orally, once or twice daily	£24 to £48

In England and Wales, over £334,000 is currently being spent on glucosamine preparations in the course of a year (including glucosamine and chondroitin preparations (ePACT July 2017 - September 2017). **Stopping prescribing of glucosamine could release savings of £334,653 across England and Wales. This equates to £571 per 100,000 patients.**

Further data available in the supporting data pack here: https://pdata.uk/#/views/B205_Glucosamine/FrontPage?:iid=2

References

1. Hunter D et al. Osteoarthritis. British Medical Journal 2006; 332: 639-642
2. Arthritis Care. Annual report. Changing the lives of people with arthritis. 2015. London: Arthritis Care. Available at: https://arthritiscare.org.uk/assets/000/001/508/Arthritis_Care_2015_Annual_Report_original.pdf?1471340573 Last accessed 28/07/2017.
3. Urwin M. et al. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. Annals of the Rheumatic Diseases 1998; 57 (11): 649–55.
4. National Institute for Health and Care Excellence (NICE). Clinical Guideline 177. Osteoarthritis: care and management. February 2014. Available at: https://www.nice.org.uk/guidance/cg177 Last accessed 28/07/2017.
5. Mason P. Dietary Supplements 2nd edition. London: Pharmaceutical Press; 2001 p118-21
6. Towheed T, Maxwell L, Anastassiades TP et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database of Systematic Reviews 2005; Issue 2, No.: CD002946. DOI: 10.1002/14651858.CD002946.pub2 updated Nov 2008.
7. Wandel S, Juni P, Tendal B et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip and knee: network meta-analysis. British Medical Journal 2010; 341: c4675
8. Black C, Clar C, Henderson R et al. The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation. Health Technol Asess 2009; Nov 13 (52): 1–148.
9. Vlad SC et al. Glucosamine for pain in osteoarthritis: why do trial results differ? Arthritis and Rheumatism 2007; 56(7):2267-2277
10. Glucosamine for knee osteoarthritis – what's new? Drug & Therapeutics Bulletin 2008; 46 (Issue 11): 81-84
11. Midlands Therapeutics Review and Advisory Committee. Glucosamine (Alateris®) for the treatment of osteoarthritis of the knee. VS 08/05, February 2008. Available at: http://ccg.centreformedicinesoptimisation.co.uk/mtrac/ Last accessed 28/07/2017.
12. Scottish Medicines Consortium - Glusartel® SMC No. 647/10 Nov 2010. http://www.scottishmedicines.org.uk/ Last accessed 28/07/2017.
13. Henrotin Y, Mobasheri A, Marty M. et al. Is there any scientific evidence for the use of glucosamine in the management of human osteoarthritis? Arthritis Research & Therapy 2012; 14; 201.
14. European Food Safety Authority. http://www.efsa.europa.eu/en
15. Messier SP, Loeser RF, Miller GD et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum. 2004 May;50(5):1501-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15146420 Last accessed 08/11/2017.
16. Huang MH, Chen CH, Chen TW et al. The effects of weight reduction on the rehabilitation of patients with knee osteoarthritis and obesity. Arthritis Care Res. 2000 Dec;13(6):398-405. Available at https://www.ncbi.nlm.nih.gov/pubmed/14635316 Last accessed 08/11/2017.
17. Toda Y, Toda T, Takemura S et al. Change in body fat, but not body weight or metabolic correlates of obesity, is related to symptomatic relief of obese patients with knee osteoarthritis after a weight control program. J Rheumatol. 1998 Nov;25(11):2181-6. Available at https://www.ncbi.nlm.nih.gov/pubmed/9818662 Last accessed 08/11/2017.
18. UKPAR. Glusartel 1500mg powder for oral solution. PL 19053/0041. MHRA, 26 Oct 2009. Available at www.mhra.gov.uk
19. Medicines and Healthcare products Regulatory Agency (MHRA). Register of SPCs and PILs - glucosamine. Available at http://www.mhra.gov.uk/spc-pil Last accessed 28/07/2017.
20. Noack W, Fischer M, Forster KK et al. Glucosamine sulfate in osteoarthritis of the knee. Osteoarthr Cartil 1994;2:51-9.

21. Reginster JY, Deroisy R,Rovati L.C. et al. Long-term effects of glucosamine sulphate on osteoarthritis progression a randomised, placebo-controlled clinical trial. Lancet 2001; 357 (9252): 251-6.
22. Scottish Medicines Consortium - Dolenio® SMC No. 729/11 Aug 2011. http://www.scottishmedicines.org.uk/
23. Medicines & Healthcare products Regulatory Agency. Current problems in pharmacovigilance – Volume 31. May 2006. Available at: http://webarchive.nationalarchives.gov.uk/20080804194642/http://mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2023859 Last accessed 28/07/2017.
24. NHS Business Services Authority (NHSBSA). Department of Health Drug Tariff. July 2017. Available at http://www.drugtariff.nhsbsa.nhs.uk Last accessed 28/07/2017.

Additional PrescQIPP resources

Briefing

Implementation resources

Available here: https://www.prescqipp.info/b205-glucosamine/category/415-glucosamine

Data pack

Available here: https://pdata.uk/#/views/B205_Glucosamine/FrontPage?:iid=2

Information prepared by Gemma Dowell, Clinical writer for PrescQIPP CIC, October 2017 and reviewed by Sue Smith, Senior Medicines Evidence Reviewer, November 2017. Non- subscribers who wish to access the implementation resources should contact help@prescqipp.info

Contact help@prescqipp.info **with any queries or comments related to the content of this document.**