PUBLIC SUMMARY DOCUMENT

Product: Glucosamine Hydrochloride, capsule, 750 mg, Arthro-Aid®

Sponsor: Arkopharma Australia Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application:

The submission sought a restricted benefit PBS listing for the symptomatic treatment of osteoarthritis.

2. Background:

This drug had not previously been considered by the PBAC.

3. Registration Status:

Arthro-Aid was registered by the TGA on 15 February 2001 for the management of osteoarthritis and the temporary relief of its associated pain.

4. Listing requested and PBAC's View

The submission requested a restricted benefit listing for the symptomatic treatment of osteoarthritis.

The PBAC noted that current guidelines and recommendations promote the use of non-pharmacological therapies and then the addition of oral analgesics (paracetamol) as first line treatment for symptomatic osteoarthritis.

5. Clinical place for the proposed therapy

The submission claimed glucosamine hydrochloride provides an alternative in osteoarthritis management to NSAIDs or selective COX-2 inhibitors.

6. Comparator

The submission nominated celecoxib as the most appropriate comparator.

The PBAC did not consider celecoxib to be the appropriate comparator. Celecoxib is specifically not subsidised for the treatment of arthrosis without an inflammatory component and the PBAC considered glucosamine is unlikely to replace celecoxib in clinical practice. The PBAC noted that current guidelines and recommendations promote the use of non- pharmacological therapies and then the addition of oral analgesics (paracetamol) as first line treatment for symptomatic osteoarthritis.

7. Clinical Trials

The submission provided both key and supportive evidence. Key evidence came from three randomised trials. The first, by Clegg et al (2006), was a 24 week comparison of glucosamine hydrochloride 1500 mg, chondroitin sulfate 1200 mg, glucosamine and chondroitin combination (1500 mg and 1200 mg respectively) and celecoxib 200 mg with placebo on participants with knee pain from osteoarthritis. This trial included a direct comparison of celecoxib against glucosamine hydrochloride via the common reference of placebo. The second trial, by Houpt et al (1999), compared glucosamine hydrochloride 1500 mg with placebo on patients with knee osteoarthritis for an 8 week blinded and an 8 week open label phase. This trial assessed the efficacy of glucosamine hydrochloride. The third trial, by Qui et al (2005), compared glucosamine hydrochloride 1400 mg and glucosamine sulphate 1500 mg (two 750 mg capsules a day) on patients with knee osteoarthritis. This trial was presented only as an English abstract.

Trial/First author	Publication title	Publication citation
GAIT/Clegg D	Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis.	New England Journal of Medicine, 2006; 354(8): 795-808
Houpt J	Effect of glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee.	Journal of Rheumatology, 1999; 26(11): 2423-2430
Qiu G-X	A multi-central randomized, controlled clinical trial of glucosamine hydrochloride/sulfate in the treatment of knee osteoarthritis.	National Medical Journal of China, 2005; 85(43): 3067-3070

Supportive evidence came from six randomised trials. Four trials compared glucosamine sulfate with ibuprofen whilst two trials compared celecoxib with ibuprofen.

8. Results of Trials

Both Clegg et al (2006) and Houpt et al (1999) measured pain change using the same validated WOMAC index[1]. Clegg et al (2006) measured the responder rate, defined as a 20% decrease in knee pain from baseline to week 24, whilst Houpt et al (1999) measured the continuous variable of the difference in change in pain score between Week 0 and Week 8.

The preliminary economic evaluation was based on the trial by Clegg et al (2006). Clegg et al. (2006) demonstrated that for all randomised patients, the rate of response (a 20% decrease in WOMAC pain score) to glucosamine hydrochloride was 3.9% higher than placebo (p=0.30), to glucosamine hydrochloride in combination with chondroitin sulfate was 6.5% higher than placebo (p=0.09), and to chondroitin sulfate alone was 5.3% higher than placebo (p=0.17). These rates were not statistically significantly different when compared to placebo. However, the rate of response to celecoxib was 10% higher than placebo and this response was statistically significant (p=0.008). The trend was the same for the secondary outcome OMERACT-OARSI[2]. Similarly, in Houpt et al (1999),

[1] Western Ontario and McMaster Universities Osteoarthritis knee and hip osteoarthritis Index

[2] Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International

glucosamine hydrochloride performed no better than placebo at reducing pain after 8 weeks of treatment.

In the key trial by Clegg et al (2006), 77 serious adverse events were reported in 61 patients. Three serious adverse events were judged by the investigators to be related to study treatment: 1 congestive heart failure (combination therapy), 1 stroke (celecoxib) and 1 chest pain (glucosamine hydrochloride). The number of patients who withdrew because of adverse events was similar among treatment and control groups in the second key trial by Houpt et al (1999).

9. Clinical Claim

The clinical claim that glucosamine hydrochloride is no worse than celecoxib in terms of effectiveness and toxicity was not considered by the PBAC to be supported by the evidence presented. The PBAC considered that the claim for non-inferiority between glucosamine hydrochloride and celecoxib was poorly supported by the key trials.

For further information see Recommendation and Reasons

10. Economic Analysis

A preliminary economic evaluation was presented. However, the PBAC agreed that the choice of the cost-minimisation approach was only valid if non-inferiority was accepted.

A modelled economic evaluation was presented and provided a cost comparison that took account of downstream health costs associated with adverse events. The base case modelled incremental savings per year were $265 per person.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed per year was > 200,000 in Year 2010. The direct financial implication of listing glucosamine hydrochloride on the PBS (considering only financial implications with glucosamine hydrochloride and celecoxib 100 mg) was cost saving to the PBS, as was the overall impact on the PBS when including savings on PPI scripts.

The DUSC advised it considered there is a likely underestimate of the number of eligible patients. The DUSC noted that in the submission the number of patients with osetoarthritis is at least 700,000 (over 65 years of age). Other information has shown that 1.8 million Australians described themselves as having ‘arthritis’ in the ABS 2003 Survey of Disability, Ageing and Carers (2). This same report noted that the 2003 survey was designed to collect information about chronic disease associated with disability and includes persons in long term residential care. DUSC considered that if 1.8 million were the eligible population, 5% penetration of this potential market would result in that range of 10 - 30 million dollars expenditure by the Government.

12. Recommendation and Reasons

The PBAC did not consider celecoxib to be the appropriate comparator. Celecoxib is specifically not subsidised for the treatment of arthrosis without an inflammatory

component and the PBAC considered glucosamine is unlikely to replace celecoxib in clinical practice. The PBAC noted that current guidelines and recommendations promote the use of non- pharmacological therapies and then the addition of oral analgesics (paracetamol) as first line treatment for symptomatic osteoarthritis.

The PBAC considered that the claim for non-inferiority between glucosamine hydrochloride and celecoxib was poorly supported by the key trials. In both trials (Clegg et al 2006, Houpt et al 1999), glucosamine hydrochloride performed no better than placebo (no statistically significant difference), whereas in Clegg et al (2006), celecoxib was found to perform better than placebo at reducing pain. More importantly, the key clinical trial suggested that there is no difference between glucosamine and placebo as no statistically significant reduction in WOMAC pain scores was found in either study for glucosamine compared to placebo.

The PBAC noted no clear evidence of excess toxicity over placebo had been demonstrated in short and long term studies with glucosamine, but that cross reactivity of shell fish allergy to glucosamine had not been well evaluated.

Therefore, the clinical claim that glucosamine hydrochloride is no worse than celecoxib in terms of effectiveness and toxicity was not considered by the PBAC to be supported by the evidence presented.

The PBAC agreed that given this finding, the economic evaluation seeking listing on a cost-minimisation basis against celecoxib had no foundation, although the Committee considered that the modelled cost comparison approach adopted was reasonable.

The PBAC also considered that multiple and appropriate issues raised by DUSC regarding the usage estimates were valid.

The PBAC rejected the submission on the basis of a lack of evidence demonstrating relevant clinical efficacy with an appropriate comparator.

13 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor is considering its position.