Public Summary Document

Product: Hylan G-F 20, injection, 16 mg in 2 mL, Synvisc®
Sponsor: Genzyme Australia Pty Ltd
Date of PBAC Consideration: March 2006

1. Purpose of Application

The submission requested listing on the Pharmaceutical Benefits Scheme (PBS) for the intra-articular treatment for osteoarthritis of the knee in patients who have not responded to non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroid injections, or are unable to take NSAIDs or receive corticosteroid injections for safety reasons.

2. Background

This was the first time hylan G-F 20 had been considered by the Pharmaceutical Benefits Advisory Committee (PBAC).

3. Registration Status

Hylan G-F 20 was registered as a device by the Therapeutic Goods Administration (TGA) on 11 December 1998.

4. Listing Requested and PBAC's View

The sponsor requested listing either in either section 85 of the PBS Schedule as a restricted benefit or authority required benefit or via a special program section 100 listing, with distribution direct to health professionals. The submission contented that the later option would result in a lower cost to Government.

Section 85 is for medicines prescribed through the community. Section 85 listings appear in the white pages of the *Schedule of Pharmaceutical Benefits*. Section 100 may be used to supply pharmaceutical benefits with special requirements. Medicines currently supplied in this way include botulinum toxin.

The wording proposed for the listing restriction was:

For the treatment, by rheumatologists, orthopaedic surgeons or radiologists of osteoarthritis of the knee in patients who have not responded to NSAIDs or corticosteroid injections, or are unable to take NSAIDs or have corticosteroid injections for safety reasons.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Hylan G-F 20 is a derivative of hyaluronan, which is the biological component responsible for viscoelasticity in the synovial fluid of the knee. Hylan G-F 20 would provide an alternative treatment for patients with osteoarthritis of the knee(s) who have exhausted all other treatment options.

6. Comparator

The submission nominated appropriate care, described by the American College of Rheumatologists, as the comparator. "Appropriate care" includes non-pharmacologic

therapies (education, support, weight loss if appropriate, physical therapy, occupational therapy and exercise programs), pharmacologic treatments and surgery.

The PBAC considered that the appropriate comparator should be all standard non-pharmacological and pharmacological therapies including NSAIDs and corticosteroid injections, s*ee Recommendations and Reasons*.

7. Clinical Trials

The submission presented 14 randomised trials comparing hylan G-F 20 and: saline or placebo (six trials); NSAIDs (two trials); intra-articular corticosteroids (two trials); "conventional" or "appropriate care" (two trials); physical therapy (one trial); and hylan G-F 20 plus arthrocentesis or two courses of hylan G-F 20 (one trial). The submission also included 17 supporting studies, comparing hylan G-F 20 and: other hyaluronic acid products (seven trials); conventional or "appropriate care" (one study); no comparator (five studies); and surgery (three studies). The PBAC considered six of the randomised trials to be key and two of the randomised trials to be supportive.

Seven of these studies, together with a meta-analysis, had been published at the time of submission.

8. Results of Trials

The outcome measures presented from the trials were "pain on weight bearing" (primary outcome) and "pain at night", which are part of the WOMAC assessment scale, (a self-administered scale which assesses the three dimensions of pain, disability and joint stiffness in knee and hip osteoarthritis using a battery of 24 questions).

The largest trial with the longest follow-up did not demonstrate a statistically significant difference between standard medical management + hylan G-F 20 and standard medical management + placebo in reduction of pain on weight bearing. There was a statistically significant difference in the primary outcomes in all other key trials.

The submission presented pooled data from a published meta-analysis. These meta-analyses pooled results from three of the key trials and from two other trials that were not evaluated separately. Pooled estimates were calculated for outcomes at a priori defined time periods post-injection.

Overall, the benefit in terms of effectiveness of standard medical management + hylan G-F 20 versus standard medical management + placebo was statistically significant but small, and although the point estimates of clinical benefit were clinically relevant, the 95% confidence intervals consistently included clinically unimportant reductions in pain according to two published reports in this area.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that hylan GF 20 had a large and highly statistically significant advantage over control therapies in alleviating symptoms of osteoarthritis. The PBAC did not accept this claim, *see Recommendation and Reasons*.

10. Economic Analysis

A preliminary (trial-based) economic evaluation was presented.

The trial-based incremental cost per extra patient with ≥20% improvement from baseline WOMAC pain score at 1 year, in study knee was < $15,000, while the trial-based incremental cost per extra QALY gained over 1 year was in the range $15,000 - $45,000.

A modelled evaluation was presented. Additional resources beyond hylan G-F 20 drug and drug administration costs include other standard medications, alternative therapy treatments, assistive devices, procedures, other therapy (acupuncture, chiropractor, exercise, massage, physiotherapy, thermal therapy, ultrasound, weight loss program), outpatient resources, hospitalisation and out-of-pocket expenses. The base case modelled incremental cost/extra patient with ≥20% improvement from baseline WOMAC score at 1 year, in study knee was < $15,000. The base case modelled incremental cost/extra QALY was in the range $15,000 - $45,000. Given the issues raised concerning observer bias with the trial, the PBAC considered these ratios to be uncertain.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the financial cost per year to the PBS was < $10 million per year in Year 3. The PBAC considered the estimates presented in the submission to be uncertain and low. The main area of uncertainty was that there may be a broader population than that intended in the proposed restriction who may be prescribed, and benefit from, hylan G-F 20, and in conjunction, that it may be difficult for Medicare Australia to restrict hylan G-F 20 to the proposed population.

12. Recommendation and Reasons

The PBAC had a number of concerned with the proposed restriction including the potential subjectivity and ambiguity of some of the requirements.

In addition, the PBAC considered that section 100 supply was not practical for a drug of this type and although savings to Government would accrue by direct supply of the product to the doctor additional expenses to Government would be incurred by Medicare Australia. Attempting to limit PBS-subsidised prescribing to certain specialists was considered to be impractical as it would be difficult for Medicare Australia to determine individual prescriber eligibility and other specialists were likely to request an expansion of the list of eligible specialities thus further expanding these difficulties.

An appropriate treatment algorithm for osteoarthritis of the knee would be a variety of non-pharmacological measures (education, quadriceps muscle strengthening, weight loss and joint protection advice) and pharmacological measures (paracetamol, NSAIDs, corticosteroid injections and possibly, glucosamine). The PBAC was concerned that the requested restriction may undo the education messages, such as appropriate use of paracetamol before attempting NSAIDs, with their associated risks.

The PBAC considered that the appropriate comparator should be all standard non-pharmacological and pharmacological therapies including NSAIDs and corticosteroid injections. The PBAC noted that potentially relevant randomised trials comparing hylan G-F 20 with these comparators were excluded from the submission.

The outcome measures presented from the trials were "pain on weight bearing" (primary outcome) and "pain at night", which are part of the WOMAC assessment scale, (a self-administered scale which assesses the three dimensions of pain, disability and joint stiffness in knee and hip osteoarthritis using a battery of 24 questions). Overall, the benefit in terms of effectiveness of standard medical management + hylan G-F 20 versus standard medical management + placebo (ie measured in trials where outcome observers were appropriately blinded) was statistically significant, but considered by the PBAC to be small and of doubtful clinical importance. The largest trial with the longest follow-up did not demonstrate a statistically significant difference between standard medical management + hylan G-F 20 and standard medical management + placebo in reduction of pain on weight bearing. Although these two outcomes are likely to be patient-relevant, there is no information on more important outcomes, such as the ability to exercise or do other activities of daily living including to maintain a job, or to use fewer rescue medications. The PBAC therefore considered that results for the complete WOMAC assessment scale would have been more informative. Furthermore, the product information document for hylan G-F 20 suggests that the best outcomes are obtained by patients who are using their joints actively, although no evidence to support this is provided in the submission. There is also no information on functionality at baseline in the trials, so it is uncertain how applying this suggestion would affect the generalisability of the trial results.

The PBAC considered that the extent of benefit derived from the pragmatic randomised trial and relied upon in the submission's economic evaluations, was overestimated. This is because the extent of benefit was measured in circumstances where not only was observer bias not minimised by blinding the patients who were the observers of the subjective measures of the outcomes to the interventions received, but observer bias is likely to have been exacerbated by the incentives offered to recruit patients into the trial forming the basis of these evaluations. Given the issues raised concerning observer bias with the trial, the PBAC considered the incremental cost-effectiveness ratios to be uncertain.

There was also uncertainty over the predicted usage of this product.

The PBAC therefore rejected the submission because of uncertain clinical benefit and uncertain and unacceptable cost-effectiveness.

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

Genzyme believes that the clinical benefit demonstarated repeatedly in well conducted clinical trials is important to individual patients. Data presented to the PBAC showed substantial pain reductions (>50%) in a significantly greater number of patients than conventional therapy.