APPENDIX Q

Evidence Review for NHS Surrey Area Prescribing Committee

Treatment: Intra-articular Hyaluronic acid & its derivatives for Osteoarthritis

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Date: For APC December 3rd 2010.

1. Purpose of the Review

To confirm a Surrey-wide position on the use of hyaluronic acid derivatives in osteoarthritis.

2. Appropriateness

2.1 The patient: patients with predominantly knee osteoarthritis

2.2 The problem:
Osteoarthritis is the most common disease of the joints, and one of the most widespread of all chronic diseases.[1] Frequently described as 'wear and tear', its prevalence increases steadily with age and by retirement age the associated radiological changes can be observed in over half the population.[1] Osteoarthritis of the knee is the result of progressive degeneration of the cartilage of the joint surface. Symptoms can vary from minimal to severe pain and stiffness, but overall the disease is responsible for considerable morbidity and is a common reason for GP consultation.[1]

2.3 The Intervention:
Hyaluronic acid and its derivatives are injected intra-articularly to supplement natural hyaluronic acid in the synovial fluid.

Hyaluronidase is an enzyme that has a temporary and reversible depolymerising effect on the polysaccharide hyaluronic acid, which is present in the intercellular matrix of connective tissue.

Care setting: secondary care
Frequency: Single injection or 1 injection weekly for 3 weeks. Effects last up to 6 to 9 monthly depending on the product, however it can be administered sooner if symptoms return.

2.4 Alternative treatments:
Treatment options depend on the severity of the osteoarthritis. The condition is usually chronic, and patients may have several treatment strategies applied at different stages. Conservative treatments include medication to relieve pain and inflammation, and physiotherapy. If there is a knee-joint effusion, fluid around the knee may be aspirated with a needle (arthrocentesis). Corticosteroids can also be administered intra-articularly. If these treatments are ineffective, a knee replacement

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operation may be necessary. Arthroscopic knee washout, with or without debridement, is also used to treat osteoarthritis of the knee.

3. Effectiveness

3.1 Expected benefits
Reduction in pain, improvement in functionality.

3.2 Is there a plausible biological basis for effectiveness?
The mechanism by which HA exerts its therapeutic effect, if any, is not certain, and evidence for restoration of rheological properties is lacking.[2] Given the relatively short intraarticular residency (hours), any hypothesis for its mechanism of action must account for the sometime reported long-duration of clinical efficacy (months).[2]

3.3 Side-effects/complications
A 2008 Royal College of Physicians review of hyaluronic acid concluded the following: "The toxicity of intra-articular HA appears small. A small percentage of patients may experience a transient increase in pain following injection, and some get a frank flare of arthritis with marked effusion. As with any injection procedure there is a very small risk of infection."[2]

3.4 Review of evidence

3.4.1 National Guidance:
NICE CG 59 – Osteoarthritis: National Clinical Guideline for Care and Management in Adults (Feb 2008):[1]

- Intra-articular hyaluronic acid (HA) is not recommended as evidence is conflicting and there are too many differences in trial design to determine true efficacy. Not considered cost-effective at this time.[1]

This recommendation was made on the basis of a review undertaken by the Royal College of Physicians which concluded that:
"The research evidence on the efficacy of HAs is often difficult to interpret because of confounders including:
_ different molecular weights of HA
_ different injection schedules (ranging from once weekly to a series of five injections)
_ poor trial design despite large numbers of studies, for example lack of intention-to-treat analyses, limitations in blinding.

On balance, the evidence seems to suggest a benefit for reducing pain up to 3 months after a series of three to five injections, although the effect size is generally small. Given this, and the cost of the therapies together with increased clinician visits required for injections, hyaluronan injections were assessed in the cost-consequence analysis.

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The Cochrane review (Bellamy 2006b) regarded pooled estimates across different products as potentially misleading, and also warned about pooled estimates because of different study designs. Also, meta-analysis was only possible for two of the WOMAC sub-scales, ruling out the use of the transfer to utility technique. With this in mind, and given the effect that different injection schedules have on cost estimates, the cost-consequence analysis looked at three products individually, using estimates from individual trials in each case. This allows a more thorough sensitivity analysis across different hyaluronan products. In all cases, the cost-effectiveness estimate is outside the realms of affordability to the NHS, and in one case is dominated by placebo. Sensitivity analyses on the individual estimates give a consistent message: that the efficacy would have to be three to five times higher than the estimates from the trials before reaching the standard threshold for cost effectiveness to the NHS.

Clinical trials do not suggest sub-groups of osteoarthritis patients may have greater benefit from HA therapies thereby improving cost effectiveness. A research recommendation is therefore made to this effect.

Recommendations
R31 Intra-articular corticosteroid injections should be considered as an adjunct to core treatment for the relief of moderate to severe pain in people with osteoarthritis.
R32 Intra-articular hyaluronan injections are not recommended for the treatment of osteoarthritis."[2]

3.4.2 Cochrane Library systematic review and meta-analysis
Seventy-six trials were identified. Follow-up periods varied between day of last injection and eighteen months. Forty trials included comparisons of hyaluronan/hylan and placebo (saline or arthrocentesis), ten trials included comparisons of intra-articular (IA) corticosteroids, six trials included comparisons of nonsteroidal anti-inflammatory drugs (NSAIDs), three trials included comparisons of physical therapy, two trials included comparisons of exercise, two trials included comparisons of arthroscopy, two trials included comparisons of conventional treatment, and fifteen trials included comparisons of other hyaluronans/hylan.

The analyses support the contention that the HA class of products is superior to placebo. There is considerable between-product, between-variable and time-dependent variability in the clinical response. The clinical effect for some products against placebo on some variables at some time points is in the moderate to large effect size range. In general, sample size restrictions preclude any definitive comment on the safety of the HA class of products, however, within the constraints of the trial designs employed, no major safety issues were detected. The analyses suggest that viscosupplements are comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events, and that HA products have more prolonged effects than IA corticosteroids. Overall, the aforementioned analyses support the use of the HA class of products in the treatment of knee OA.[3]

PCT comment: this Cochrane review was taken into account in the RCP/NICE recommendations in section 3.4.1 above.

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3.4.3 Bandolier

Intra-articular hyaluronic acid for knee osteoarthritis:

Clinical bottom line:There is no evidence from good quality trials that intra-articular hyaluronic acid is effective.

3.4.4 Canadian Agency for Drugs and Technologies in Health reviews

Knee Osteoarthritis:

A 2007 review suggested modest efficacy of hyaluronic acid compared with placebo in knee osteoarthritis:[4]

The main relevant points are below:

- Small but significant clinical effect (wrt pain/function) of HA compared with placebo – similar to NSAIDs ∴probably only appropriate in patients who can not tolerate other treatment.
- Does not appear to modify the course of the disease
- Slower onset compared with IA corticosteroids but effects may last longer
- Marked variation in effects depending on study (possibly due to product used, outcome measures, time of measurement)
- Some specific evidence for individual products compared with placebo:
  - Hyalgan and Synvisc – positive evidence
  - Supartz and OrthoVisc – positive but weaker evidence
  - Durolane, Fermathron and Ostenil – insufficient evidence
  - Suplasyn – no positive evidence

  PCT comment: Hyalgan is a blacklisted product e.g. not prescribable on the NHS. Supartz is not available in the UK.

  However the above variation may be due to study design.
- May be more effective in patients under 65 years with mild/moderate effusion and pain (suggested from a review of 6 systematic reviews)
- Some suggestion that higher molecular weight HA may be more effective (conflicting evidence). However, acute severe inflammatory reactions may be more common with these products. [4]

Hip Osteoarthritis

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The Canadian Agency for Drugs and Technologies in Health (CADTH) also published a review on intra-articular hyaluronic acid (HA; viscosupplementation) for hip osteoarthritis (OA) in 2007. The authors discuss the results of two systematic reviews and two randomised controlled trials, and briefly the findings of smaller open-label trials.

In summary:

• Two systematic reviews found that HA for hip OA may relieve pain and improve function. Randomised controlled trials had differing results. Uncontrolled studies suggest that there are moderate improvements regarding pain and function for three to six months after HA injection.

• The best available evidence suggests that HA may offer symptomatic relief in patients with mild to moderate hip OA for whom other conservative therapies are contraindicated or have failed. Currently, there is insufficient good quality evidence to determine this conclusively.

• No serious adverse events have been reported after intra-articular injection of HA for hip OA.

• There is no evidence regarding the cost-effectiveness of this therapy.[5]

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4. Summary of Key Points for Consideration

4.1 National guidance: NICE CG 59 does not recommend the use of hyaluronan derivatives in osteoarthritis.

4.2 Efficacy
There is conflicting evidence regarding the effectiveness of the intervention and there appears to be differences between different products.

4.3 Potential Benefits over existing therapy
No proven benefit over intra-articular corticosteroids

4.4 Potential disadvantages
Variability between products, less evidence of proven efficacy.

4.5 Budgetary Impact

4.5.1 Cost: The drug cost will be included within tariff for an orthopaedic outpatient appointment (same cost therefore as if an intra-articular corticosteroid is given as per NICE CG59).

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APPENDIX Q

Consultant-led first-attendance: £135
Follow-up appointments: £72
(HRG4 2009/10 prices)

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APPENDIX Q

Table 1. Cost of individual hyaluronan products (classified under Part IXA of the Drug Tariff: Approved list of appliances

Product	Manufacturer	Presentation	Dose	Cost /syringe (October 2010 Drug Tariff)
Arthrum H	Dee pharmaceuticals	40mg/2ml syringe	1 syringe at weekly intervals for 3 weeks. Lasts 6-9 months according to manufacturer.	£58.33 + VAT
Arthrum 2.5%	Dee pharmaceuticals	75mg/3ml syringe	Single injection. Lasts 6-9 months according to manufacturer.	£175 + VAT
Durolane	Smith and Nephew (Q-Med UK)	60mg/3ml syringe	1 syringe (into synovial joint including knee or hip) 6 monthly	£195.74 + VAT
Euflexxa	Ferring	20mg/2ml syringe	1 syringe into the knee at weekly intervals for 3 weeks. Effective for minimum 12 weeks according to Ferring.	£195.00 + VAT
Fermathron	Biomet Europe	20mg/2ml syringe	Once/week injection to max. 3-5 doses.	£39.00 + VAT
Orthovisc	Surgicraft	1.5% syringe	1 injection to the knee per week for 3-4 doses. Effective for up to 6 months according to Surgicraft.	£65.00 + VAT
Ostenil	TRB Chemidica (UK) Ltd	20mg/2ml syringe	1 injections one week apart for 3 weeks in mild-moderate RA repeated as required (usually 6-monthly according to Chemidica).	£33.00 + VAT
Ostenil Plus	TRB Chemidica (UK) Ltd	40mg/2ml syringe (extended release formulation)	Usually given as single injection (licensed for up to 3).	£80.00 + VAT
Suplasyn	Teva	20mg/2ml syringe		£35.49 + VAT
Synvisc (hylan GF-20)	Genzyme Therapeutics Ltd	16mg/2ml syringe for knee, ankle, shoulder and hip.	Knee - one injection/week for 3 weeks. A maximum of 6 injections may be given with a minimum of 4 weeks between treatment regimens. Hip, ankle and shoulder - one injection only. If response is inadequate this may be repeated 1-3 months after the initial injection.	£68.33 + VAT for 1 syringe for ankle, shoulder or hip.
Synvisc One(hylan GF-20)	Genzyme Therapeutics Ltd	48mg/6ml syringe for knee.	Knee - one injection only. This can be repeated 6 months after first injection.	£205.00 + VAT

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4.5.2 Precedent setting:

NHS Surrey Orthopaedic Network
Minutes of meeting June 30th 2010:
Low Priority Procedure List: Hyaluronic Acid injections

- Agreed that in keeping with NICE Guidance this should be added to the 'black' (not funded) medicines list and included within the LPP
- Proposed that Medicines Management also follow this up among rheumatology colleagues.

NHS Surrey Rheumatology Meeting 17/11/2010:
Only supported the use of hyaluronic acid in very limited cohort of defined patients: those who are unsuitable for joint replacement surgery in which there are no other available treatment options.

Other NHS Commissioning Organisations
East Midlands Specialised Commissioning Group: not routinely funded
Dudley PCT: not routinely funded

5. Conclusions and Recommendations
There is conflicting evidence that hyaluronic acid intra-articular injections may be of clinical benefit in osteoarthritis and particularly in the knee joint. The treatment is not, however, sufficiently cost-effective to recommend its routine use in the NHS.

Options for Consideration

1. It is recommended that NHS Surrey supports the recommendations set out in NICE CG59:
   Intra-articular hyaluronic acid (HA) is not recommended as evidence is conflicting and there are too many differences in trial design to determine true efficacy. Not considered cost-effective at this time.

It may be suitable for individual patients for whom other pharmacological options have been intolerable or ineffective and who are unable to undergo surgery. Hyaluronic acid for these patients should be made available on an individual basis.

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APPENDIX Q

Appendix 1: Evidence search

Search terms used:

Resource	Used in this review?
National Library for Health (NHL) http://www.library.nhs.uk/Default.aspx A gateway site with access to other resources such as Reviews (Bandolier, Cochrane, CRD etc), Guidelines (e.g. NICE), Clinical Knowledge Summaries (CKS) and Journals including AMED, British Nursing Index, CINAHL, E-books, EMBASE, HMIC, MEDLINE, My Journals, PsycINFO, PubMed, Databases from Dialog.	✓
National Institute of Health and Clinical Excellence (NICE) http://www.nice.org.uk/ NICE produces national guidance in three areas of health: 1. Public health - guidance on the promotion of good health and the prevention of ill health 2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS 3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS.	✓ (through NHL)
Bandolier http://www.medicine.ox.ac.uk/bandolier/index.html Bandolier is a website about the use of evidence in health, healthcare, and medicine. Information comes from systematic reviews, meta-analyses, randomised trials, and from high quality observational studies.	✓(through NHL)
Centre for Reviews and Dissemination http://www.york.ac.uk/inst/crd/ CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care. Databases maintained by CRD include Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database	✓(through NHL)
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/ Scottish equivalent of NICE	✓
Medical Services Advisory Committee (Australia) http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home-1 The principal role of the Medical Services Advisory Committee (MSAC) is to advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures.	✓
Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/index.php/en/home The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.	✓

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Appendix 3: References

1. National Institute for Health and Clinical Effectiveness. Clinical Guideline 59. Osteoarthritis – national clinical guideline for care and management in adults. February 2008. Available from: http://www.nice.org.uk/nicemedia/live/11926/39557/39557.pdf Accessed 25/10/2010.

2. The National Collaborating Centre for Chronic Conditions/Royal College of Physicians. Osteoarthritis – national clinical guideline for care and management in adults. 2008. Available from: http://www.nice.org.uk/nicemedia/live/11926/39720/39720.pdf. Accessed 25/10/2010

3. Bellamy N et al. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database of Systematic Reviews, 2006, Issue 2. Art. No.: CD005321. DOI:10.1002/14651858.CD005321.pub2.

4. Dagenais S. *Intra-articular hyaluronic acid (viscosupplementation) for knee osteoarthritis.* [Issues in emerging health technologies issue 94]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006. Available from: http://www.cadth.ca/media/pdf/E0010_viscosupplementation_cetap_e.pdf. Accessed 13/07/2010.

5. Canadian Agency for Drugs and Technologies in Health. Intra-articular hyaluronic acid for hip osteoarthritis. Issue 98. May 2007. Available from: http://www.cadth.ca/media/pdf/E0024_viscosupplementation_cetap_e.pdf. Accessed 13/07/2010.

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