Health Technology Clinical Committee
Findings and Coverage Decision
Topic: Hyaluronic Acid / Viscosupplementation
Meeting Date: May 14, 2010
Final Adoption: August 20, 2010

Number and Coverage Topic
20100514A – Hyaluronic Acid / Viscosupplementation

HTCC Coverage Determination

Hyaluronic Acid / Viscosupplementation is a covered benefit with conditions consistent with the criteria identified in the reimbursement determination.

HTCC Reimbursement Determination

❖ Limitations of Coverage
Hyaluronic Acid / Viscosupplementation coverage: Based on the evidence about the technologies’ safety, efficacy, and cost-effectiveness, Hyaluronic Acid / Viscosupplementation is a covered benefit for the treatment of pain associated with Osteoarthritis (OA) of the knee when all of the following conditions are met:
❖ In patients who have not had an adequate response to nonpharmacological conservative treatment and simple analgesics;
❖ Is limited to two courses per year with at least four months between courses; and
❖ Documented evidence of clinical benefit from the prior course of treatment is required for subsequent treatment courses.

❖ Non-Covered Indicators
❖ All other joints

❖ Agency Contact Information

<table>
<thead>
<tr>
<th>Agency</th>
<th>Contact Phone Number</th>
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<tbody>
<tr>
<td>Labor and Industries</td>
<td>1-800-547-8367</td>
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<tr>
<td>Public Employees Health Plan</td>
<td>1-800-762-6004</td>
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<tr>
<td>Health and Recovery Services Administration</td>
<td>1-800-562-3022</td>
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**Health Technology Background**

The Hyaluronic Acid / Viscosupplementation topic was selected and published in December 2009 to undergo an evidence review process. Hyaluronic Acid / Viscosupplementation for Osteoarthritis (OA) of the Knee impacts 27 million adults in the United States, and the most commonly affected joint is the knee, with prevalence estimates ranging from 12% to 16%. OA of the knee may affect 37% of the over 60 year old population. To date, there is no known cure for OA nor is there a disease-modifying agent. OA knee problems may involve a decreased level of synovial fluid in the joint, as well as loss of cartilage and inflammation. Optimal management generally requires a combination of both nonpharmacological and pharmacological therapies. Pharmacological therapy generally begins with Acetaminophen → nonsteroidal anti-inflammatory drugs (NSAIDs) → intraarticular (IA) corticosteroid → total knee replacement (TKR). Management options include: lifestyle changes – physical therapy and exercise; systemic and topical analgesics; bracing/orthotics; corticosteroid and ACS injections; alternative and complementary therapy; and surgical joint replacement.

Viscosupplementation with hyaluronan has been introduced as an alternative to NSAIDs or intra-articular injection therapy for OA. Hyaluronans are also known as sodium hyaluronate or hyaluronic acid (HA). HA is a natural component of synovial fluid and lubricates joints and provides shock absorption which may decrease with OA. HA passes through joints cyclically, with residence in joint typically not more than hours to days. Hyaluronic products can be characterized by varying molecular weight and on the course per treatment injections.

In March 2010, the HTA posted a draft and then followed with a final report from a contracted research organization that reviewed publicly submitted information; searched, summarized, and evaluated trials, articles, and other evidence about the topic. The comprehensive, public and peer reviewed Hyaluronic Acid / Viscosupplementation report is 95 pages, and identified a relatively large amount of literature.

An independent group of eleven clinicians who practice medicine locally meet in public to decide whether state agencies should pay for the health technology based on whether the evidence report and other presented information shows it is safe, effective and has value. The committee met on May 14th, reviewed the report, including peer and public feedback, and heard public and agency comments. Meeting minutes detailing the discussion are available through the HTA program or online at [http://www.hta.hca.wa.gov](http://www.hta.hca.wa.gov) under the committee section.
Committee Findings

Having considered the evidence based technology assessment report and the written and oral comments, the committee identified the following key factors and health outcomes, and evidence related to those health outcomes and key factors:

1. Evidence availability and technology features

The committee concludes that the best available evidence on hyaluronic acid / viscosupplementation has been collected and summarized. The evidence is presented below:

- Osteoarthritis (OA) is the most common form of chronic articular disease. OA affects approximately 27 million adults in the United States. The most commonly affected joint is the knee, with prevalence estimates ranging from 12% to 16%. To date, there is no known cure for OA nor is there a disease-modifying agent. Optimal management generally requires a combination of both nonpharmacological and pharmacological therapies, and joint replacement surgery or a joint salvage procedure may be considered for selected patients with severe symptomatic OA who have not obtained adequate pain relief and functional movement from medical therapy.

- Viscosupplementation with hyaluronan has been introduced as an alternative intraarticular injection therapy for OA. Hyaluronans are also known as sodium hyaluronate or hyaluronic acid (HA). HA is a normal component of synovial fluid and cartilage. The viscous nature of the compound allows it to act as a joint lubricant, whereas its elasticity allows it to act as a shock absorber. Hyaluronic products are characterized by their molecular weight, which varies according to the source of the compound and method of preparation.

- Hyaluronate preparations have been approved by the Food and Drug Administration (FDA) for treatment of pain associated with OA of the knee in patients who have not had an adequate response to nonpharmacological, conservative treatment and simple analgesics.

- Systematic Reviews: The evidence based technology assessment report focused on three systematic reviews concerned primarily with the efficacy of viscosupplementation (Bellamy, 2006; Hayes, 2009 and Samson, 2007); a systematic review of trials comparing hylan with HA (reichenback, 2007); and a systematic review of trials comparing HA or hylan with corticosteroids (Bannuru, 2009).

- Literature Search: The evidence based technology assessment report also conducted a literature search for evidence after the systematic reviews which yielded four RCTs published later than the last search date in the systematic reviews. These included two placebo-controlled trials (Altman, Rosen, Bloch, Hatoum and Korner, 2009; Baltzer, Moser, Jansen and Krauspe, 2009), a head-to-head comparison between hylan and non-cross-linked HA (Chou, Lue, Lee, Lin and Lu, 2009), and a head-to-head comparison between HA and exercise with placebo control (Kawasaki, 2009).
Cost and cost-effectiveness data: were available in three systematic reviews (Hayes, 2009; VA, 2008; Waddell, 2007), and an additional two primary economic studies were selected from the National Health Service (NHS) Economic Evaluation Database (EED) (Kane, and Clarke, 2008; Turajane, Labpiboonpong and Maungsiri, 2007). Data from a cost-effectiveness analysis was abstracted from one of the selected guidelines (NICE, 2008).

The evidence based technology assessment report identified 6 expert treatment guidelines and no national Medicare policy relating to hyaluronic acid.

The committee also reviewed information provided by the state agencies, and public members; and heard comments from the evidence reviewer, HTA program, the public and agency medical directors.

2. **Is the technology safe?**

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is safe. Summary of committee considerations follows.

- The overall strength of evidence regarding safety is moderate quality. Trial design (RCT), sample size and outcome measures limit identification of harms, however other trials and registries support similar findings of rare serious events (psuedosepsis) and common minor local reactions.
- The Hayes and Bellamy reviews described adverse events as occurring at very low rates in RCTs. The Samson review, on the other hand, described minor adverse events as “common” and serious events as rare, using event rates from large case series.
- Intraarticular injections, including viscosupplementation, carry a risk of local, transient reactions (in the range of 2% of patients in a single course of treatment). Serious adverse events include psuedosepsis, and are rare (less than 1%).
- There is some evidence that repeat courses of treatment result in increased risk (in the range of 8% of patients) of adverse events, at least with the use of hylan.

3. **Is the technology effective?**

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is effective. Summary of committee considerations follows.

- The evidence based technology assessment report and committee discussion focused on a recent Agency for Healthcare Research and Quality (AHRQ) technology assessment (Samson, 2007) that summarized six meta-analyses. A total of 5,843 patients and 42 placebo-controlled RCTs are represented in the Samson review of meta-analysis. In addition, Samson performed several additional analyses on data abstracted from one of the reviewed meta-
analysis: the Cochrane Review (Bellamy, 2006). Each of the six meta-analyses calculated pooled estimates for multiple follow-up intervals. Additionally, the evidence based technology assessment report identified 4 subsequent randomized trials, one of which (Altman 2009) was discussed extensively by the committee.

- The authors of the 5 meta-analysis summarized in the Samson review came to a variety of conclusions ranging from negative, to moderately positive, to strongly positive. The Samson reviewers concluded that only one meta-analysis had data to fully support their conclusion, which was that HA has not been proven effective; and Samson review itself concluded clinical benefit for HA not yet clearly demonstrated.

- The evidence based technology report concluded that there was overall moderate quality of the body of evidence about efficacy, with approximately 50 RCTs comparing HA with placebo, consistently finding statistically significant differences in pain and function, especially during ~1 to 2 months after treatment.

- The evidence based technology report further concluded, that though consistent, the pain benefit may not be clinically important. Weighted mean differences ranged from 1 to 22 on a 100 point scale; with greater than 20 generally accepted as a minimum clinical effect. Weighted mean differences reported by meta-analyses were 7.3 at 22-30 weeks and 9.0 at 14 to 26 weeks, but no treatment effect was observed at 12 weeks. Standardized effects sizes in Bellamy were 0.8 where convention was that .3 is small; .5 is moderate; and .8 is large.

- The difficulty with the reporting in these trials is that a small mean effect does not convey whether only a few patients or a substantial portion of patients experienced improvement, and at what level (e.g. clinical significance).

- The two later RCTs related to efficacy of HA compared to placebo had conflicting results with one showing no statistical difference and one RCT demonstrating efficacy at 26 weeks (Altman, 2009) with an adjusted mean difference in change in pain score of 8.8; which was similar to the meta analysis. Percent of individuals were also calculable for each arm, with: 58% in HA arm and 46% in Saline(placebo) arm achieving greater than 20 point improvement at 26 weeks (an odds ratio of 1.7), though non-significant at 12 weeks. Altman, rated as a good quality study, is a 36-site double blind, randomized trial with 588 participants, funded by industry (open label).

- The committee discussed the Altman trial; both as confirmatory of the body of literature suggesting benefit, and a continuation of the troubling reporting in mean effect size which makes evaluation of the magnitude of benefit difficult.

- Comparison with other therapies: the evidence based technology report indicates generally limited evidence comparing HA to alternatives:

- One systematic review (Hayes) reported comparisons with NSAIDs, appropriate care only, exercise, and intraarticular corticosteroids, the results were either conflicting or available from a single trial.
Another review (Bellamy) reported 6 RCTs comparing HA with NSAIDs and found two treatments had comparable efficacy; and 7 RCTs with corticosteroids where HA appeared to confer a delayed but longer term benefit.

A double-blind RCT of good quality compared autologous conditioned serum (ACS) with HA and with saline placebo (Baltzer, Moser, Jansen and Krauspe, 2009). ACS was found to have a substantial effect on function, pain, and quality of life (QOL) at 7, 13, and 26 weeks, compared with both HA and with placebo. In a fair quality trial, differences between HA and placebo and home exercise were small and non-significant.

- The evidence based technology assessment report indicated that there were fewer meta-analyses of functional outcomes than of pain outcomes. Of 15 analyses reported in the Samson review, 9 were significant and favorable, and again, those were for the longer follow-up periods. Effect sizes for function outcomes ranged from 0.16 at best in one meta-analysis to 0.32 in another meta-analysis to ≥ 0.8 in the Bellamy review.

- Overall, high consistency of positive, though not always statistically or clinically significant benefit. Limitations of evidence included lack of reporting in useful terms; poorer trial quality; small sample sizes; outlier trials; protocol for use of escape medicine; patient age over 65; inconsistent methods and 55% of trials funded by industry. Unanswered questions regarding the role of the therapy (as replacement or addition) and the effect of combination with other therapies; the potential to delay surgical intervention; the length of pain relief and measures other than pain relief.

### 4. Special Populations?

- The evidence based technology reported rated overall strength of evidence as low quality with very few data studies available. Most subgroup analyses were based on post hoc subgroup analysis. No evidence based conclusions could be drawn regarding the differential effectiveness of viscosupplementation by age, race/ethnicity, gender, primary vs. secondary OA, disease severity and duration, weight (BMI), and prior treatments because of a paucity of data. Individual trial evidence regarding the influence of age and disease severity has been conflicting, but a meta-regression and subgroup analysis of 20 trials suggested that younger age predicts greater response. Factors other than age or disease severity have either not been studied or have been shown by one or two studies to be unrelated to treatment effect.

- One meta-analysis of 20 trials (Wang, 2005) included in the Samson review assessed the influence of patient factors on the treatment effect of HA (versus placebo). Using meta-regression and subgroup analysis, the authors found greater mean patient age to be associated with smaller treatment effect. However, (see below) this effect was not replicated in a follow on trial.
The evidence based technology report indicated a Samson trial (also described in the Hayes review) comparing intraarticular HA with placebo found no overall treatment effect but did observe a significant effect in a subgroup of patients who were > 60 years of age and had more severe OA (Lequesne Index scores > 10). This finding was not replicated in a confirmatory study. Two RCTs failed to detect a differential effect according to age, sex, or body mass index (BMI)/weight. One of these two trials also failed to detect a differential effect by disease severity.

Differential by product or molecular weight: some head to head comparator trials were included in the overall Bellamy review, but authors concluded that they were too few in number to allow conclusions about the relative value of hylan over non-hylan HA or of any HA product compared to another. Four meta-analysis reported in Samson showed evidence that hylan had a superior effect to non-hylan products but a fifth meta analysis did not show differences and all analysis were indirect comparisons. Further, sensitivity analysis suggested significant heterogeneity and when poor quality trials were removed, pooled effect sizes did not cross the confidence interval. Similarly, Reichenbach analyzed differences in molecular weight and detected no statistically significant differences.

5. Is the technology cost-effective?
The committee discussed multiple key factors that were important for consideration in their overall decision on whether the technology has value and is cost-effective. Summary of committee considerations follows:

The evidence based technology report cited the following cost information (Hayes, 2009), obtained from the website of a supplier (Axon Medical Supplies):
- Hyalgan: $69 for one 2.0-mL syringe; 10 syringes for $570.
- Orthovisc: $706.27 for one 2.0-mL syringe; three syringes or 10 ampules for $1,950.
- Supartz: $318.99 for five 2.5-mL syringes.

The evidence based technology report indicated cost estimates from the Veterans Administration and Department of Defense, from the perspective of a payer/healthcare system (VA, 2008):
- Euflexxa: $87 per injection, $260 per course of treatment (three injections).
- Hyalgan: $65 per injection, $195 to $325 per course of treatment (three to five injections).
- Orthovisc: $198 per injection, $595 to $793 per course of treatment (three to five injections).
- Supartz: $68 per injection, $205 to $341 per course of treatment (three to five injections).
- Synvisc: $142 per injection, $426 per course of treatment (three to five injections).
• Washington State Agency utilization and cost information indicated rising utilization; annual costs at $1.2 million and per treatment cost of $665.00.
• The evidence based technology report included an economic analysis conducted by NICE related to their OA guidelines (NICE, 2008), which concluded that efficacy would have to be three to five times higher than estimates from trials before reaching standard threshold for cost effectiveness to the NHS.
• The evidence based technology report found only two pragmatic cost studies of low quality (societal perspective, Canada and France) which reported an acceptable one-year cost-utility ratio for the addition of HA to appropriate care at $10,000 CAD in 1999 costs or similar cost and improved effectiveness when hylan was compared with conventional care. The results should be interpreted in light of the fact that comparisons of HA with placebo have generally shown less than clinically significant treatment effects.
• Evidence pertaining to the cost-effectiveness of HA has several deficiencies: time frames were short (six months to one year); the number of cost analyses and cost-effectiveness studies is very small and estimates of clinical benefit cannot be assessed due to the paucity of comparable data; there were no cost data or cost-effectiveness data specific to single-injection treatments, now possible for at least one product (FDA, 2010); the full economic evaluations were not conducted in the United States, the results may not apply to U.S. due to differences in prices, reimbursement policies, standards of care, and definitions of cost-effectiveness limits; and there was no cost-effectiveness analysis of HA versus intraarticular corticosteroid injection.

6. Medicare Decision and Expert Treatment Guidelines
Committee reviewed and discussed the expert guidelines as identified and reported in the technology assessment report.
• Centers for Medicare and Medicaid Services – no national Medicare coverage policy.
• Guidelines - a search of the core sources and relevant specialty groups identified six publications from within the past ten years that addressed hyaluronic acid / viscosupplementation for OA of the knee (AAOS, 2008; ACR, 2000; APS, 2002; NICE, 2008; VA, 2008; and Zhang, 2007, 2008).
• Three guidelines rated high quality based on modified AGREE international checklist for evidence based guidelines are summarized:
  o (1) Osteoarthritis Research Society International (OARSI), 2007 and 2008 – injections of intraarticular hyaluronate may be useful in patients with knee OA (level of evidence, strength of recommendation 64% [95% CI, 43-85]). They are characterized by delayed onset, but prolonged duration, of symptomatic benefit when compared with intraarticular injections of corticosteroids.
Superseded by determination #20131114A
Hyaluronic Acid/ Viscosupplementation

- (2) American Academy of Orthopaedic Surgeons (AAOS), 2008 – concluded that they could not recommend for or against the use of intraarticular hyaluronic acid for patients with mild to moderate symptomatic OA of the knee (level of evidence I and II; grade of recommendation inconclusive).

- (3) National Institute for Clinical Health and Excellence (NICE), 2008 – intraarticular hyaluronan injections are not recommended for the treatment of OA of the knee, or any other joint.
  - Three guidelines rated low quality based on modified AGREE international checklist for evidence based guidelines supported use of OA for knee pain.

**Committee Decision**
Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and agency and state utilization information. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

The committee concluded unanimously that the current evidence on Hyaluronic Acid / Viscosupplementation demonstrates that there is sufficient evidence to indicate that hyaluronic acid / viscosupplementation is equally safe to alternative treatments. The majority of the committee concludes that the comprehensive evidence shows that hyaluronic Acid / Viscosupplementation is a more effective treatment than treatment without HA for OA of the knee. The committee agreed that no compelling evidence exists to differentiate sub groups or special populations. The committee concludes that the HA/Viscosupplementation is unproven to be cost effective; agreeing with the comprehensive evidence review that no evidence based conclusions about cost effectiveness can be drawn.

Based on the deliberations the committee concluded that the current evidence on Hyaluronic Acid / Viscosupplementation demonstrates that there is sufficient evidence to cover with conditions the use of Hyaluronic Acid / Viscosupplementation for the treatment of pain associated with OA. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted 7 to 3 to cover with conditions Hyaluronic Acid / Viscosupplementation. Hyaluronic Acid / Viscosupplementation is a covered benefit for the treatment of pain associated with Osteoarthritis (OA) of the knee when all of the following conditions are met:
  - In patients who have not had an adequate response to nonpharmacological conservative treatment and simple analgesics;
  - Is limited to two courses per year with at least four months between courses; and
- Documented evidence of clinical benefit from the prior course of treatment is required for subsequent treatment courses.

Additional Committee comments: The committee also unanimously agreed that the evidence does not currently demonstrate that any one hyaluronic acid product or administration protocol is superior.

Health Technology Clinical Committee Authority
Washington State’s legislature believes it is important to use a scientific based, clinician centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority, through its Health Technology Assessment program to engage in a process for evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company and takes public input at all stages. Pursuant to RCW 70.14.110 a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State Health Technology Clinical Committee (HTCC), determines how selected health technologies are covered by several state agencies. RCW 70.14.080-140. These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases their decisions on evidence of the technology’s safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Administrator.