



Health Technology Clinical Committee**Date: May 14, 2010****Time: 8:00 am – 3:30 pm****Location: Marriott Hotel – 3201 South 176th Street, Seattle, WA 98188****Teleconference Bridge: 1-218-936-4700 Access Code: 9461464****Adopted: August 20, 2010****HTCC MINUTES**

Members Present: Brian Budenholzer; Michael Myint; Carson Odegard; Richard Phillips; C. Craige Blackmore; Louise Kaplan; Megan Morris; Christopher Standaert; Michelle Simon and Kevin Walsh.

Absent: Michael Souter

HTCC FORMAL ACTION

1. **Call to Order:** Dr. Budenholzer, Chair, called the meeting to order. Sufficient members were present to constitute a quorum.
2. **November 20th, 2009 Meeting Minutes:** Chair referred members to the draft minutes; motion to approve and second, and adopted by the committee.
 - *Action: Eight committee members approved the November 20th, 2009 meeting minutes, as amended to make minor corrections. One committee member abstained from voting. Amendment to include an editorial correction.*
3. **Cardiac Artery Calcium Scoring (CACS) draft Findings & Decision:** Chair referred members to the draft findings and decision and called for further discussion or objection. The Cardiac Artery Calcium Scoring findings & decision was approved and adopted by the committee.
 - *Action: Eight committee members approved the Cardiac Artery Calcium Scoring findings & decision document. One committee member abstained from voting. Amendment to include an editorial correction.*
4. **Hip Resurfacing draft Findings & Decision:** Chair referred members to the draft findings and decision and called for further discussion or objection. The Hip Resurfacing findings & decision was approved and adopted by the committee.
 - *Action: Eight committee members approved the Hip Resurfacing findings & decision document. One committee member abstained from voting.*
5. **Hyaluronic Acid / Viscosupplementation:** The HTCC reviewed and considered the Hyaluronic Acid / Viscosupplementation technology assessment report; information provided by the Administrator; state agencies; public members; and heard comments from the evidence reviewer, HTA program, the public and agency medical directors. 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.

HTCC COMMITTEE COVERAGE DETERMINATION VOTE			
	Not covered	Covered Unconditionally	Covered Under Certain Conditions
Hyaluronic Acid / Viscosupplementation	3	0	7

- *Action:* The committee chair directed HTA staff to prepare a Findings and Decision document on Hyaluronic Acid / Viscosupplementation reflective of the majority vote.
- Limitations of 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:
 1. In patients who have not had an adequate response to nonpharmacological conservative treatment and simple analgesics;
 2. Is limited to two courses per year with at least four months between courses; and
 3. 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.



SUMMARY OF HTCC MEETING TOPICS, PRESENTATION, AND DISCUSSION

Agenda Item: Welcome & Introductions

- ✓ The Health Technology Clinical Committee (HTCC) met on May 14th, 2010.

Agenda Item: Meeting Open and HTA Program Update

Dr. Brian Budenholzer, HTCC Chair, opened the public meeting.

- ✓ Leah Hole-Curry, HTA Program Director, provided an overview of the agenda, meeting guide and purpose, room logistics and introductions.

Agenda Item: Previous Meeting Business

November 20th, 2009 Meeting Minutes: Chair referred members to the draft minutes and called for a motion and discussion. Minutes were circulated prior to the meeting and posted. The adoption amendment includes an editorial correction.

- *Action: Eight committee members approved, as amended, the November 20th, 2009 meeting minutes. One committee member abstained from voting. Amendment to include an editorial correction (found on page 16, bullet #3.1).*

Cardiac Artery Calcium Scoring (CACS) Findings and Decision: Chair referred members to the draft findings and decision and called for further discussion. The draft findings and decision document was circulated prior to the meeting and posted to the website for a two week comment period. No public comments were received by the program during the publication of the CACS draft findings and decision.

- *Action: Eight committee members approved the Cardiac Artery Calcium Scoring findings & decision document. One committee member abstained from voting. Amendment to include an editorial correction (found on page 3, bullet #3.1).*

Hip Resurfacing draft Findings & Decision: Chair referred members to the draft findings and decision and called for further discussion or objection. The Hip Resurfacing findings & decision was approved and adopted by the committee.

- *Action: Eight committee members approved the Hip Resurfacing findings & decision document. One committee member abstained from voting.*

Agenda Item: Hyaluronic Acid / Viscosupplementation Topic Review

Leah Hole-Curry, HTA Program Director, introduced the technology topic up for discussion:

- ✓ Hyaluronic Acid / Viscosupplementation: review of the evidence of the safety, efficacy and cost-effectiveness of Hyaluronic Acid / Viscosupplementation for osteoarthritis (OA) of the knee.

Hyaluronic Acid / Viscosupplementation –



- ✓ OA affects around 27 million people (US); OA is progressive and has no cure. OA of the knee may affect 37% of the over 60 year old population.
- ✓ 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.
- ✓ OA knee problems may involve a decreased level of synovial fluid in the joint, as well as loss of cartilage and inflammation.
- ✓ Varying HA types of treatment strategies: cross-linked derivative vs. natural; different molecular weights; and 1 to 3 to 5 injections per course of treatment.
- ✓ 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.
- ✓ Intra-articular injection of HA categorized as a biological device, first FDA approval in 1997.
 - Treatment of pain associated with knee OA; patients who have not responded adequately to conservative non-pharmacologic therapy (physical therapy) or simply analgesics (acetaminophen).
 - Contraindications: known allergy to hyaluronate preparations, or to birds or bird products; or infections or skin diseases at the injection site of knee joint.
 - Off label: reports of use in hip, ankle, shoulder and other joints; retreatment.
- ✓ Technology dissemination – rapid uptake in past several years, especially newer products; escalating utilization.
- ✓ Potential Benefits – pain relief and functional improvement.
- ✓ Potential Drawbacks – treatment is additive; uncertain benefit and duration; injection related harms; and cost.
- ✓ Prioritization Criteria Review – Safety = Low; Efficacy = Medium; and Cost = High.
- ✓ Medicare Coverage and Clinical Guidelines:
 - There is no Medicare National coverage decision on Hyaluronic Acid / Viscosupplementation.
 - Hyaluronic Acid Clinical Guidelines – 6 guidelines identified by evidence center:
 - American College of Rheumatology (ACR), 2000 – Intraarticular hyaluronan therapy is indicated. Quality = Poor.
 - American Pain Society (APS), 2002 – Injection of HA supplements into the knee may be considered in persons with OA. Quality = Poor.
 - American Academy of Orthopaedic Surgeons (AAOS), 2008 – concluded they could not recommend for or against as evidence is inconclusive. Quality = Good.
 - National Institute for Clinical Health & Excellence (NICE), 2008 – Intraarticular hyaluronan injections are not recommended for the treatment of OA of the knee, or any other joint. Quality = Good.



- Veterans Health Administration (VA), 2008 – Evidence supports the use of intraarticular hyaluronan or hylan injections for OA of the knee. Quality = Poor.
- Osteoarthritis Research Society International (OARSI), 2008 – Injections of intraarticular hyaluronate may be useful in patients with knee OA. Quality = Good.

Agenda Item: Public Comments

The Chair called for public comments.

- ✓ Scheduled Public Comments: Four stakeholder groups requested scheduled time for public comments.
 - Bill Struyk, DePuy-Mitek, described other payer policies that cover Hyaluronic Acid / Viscosupplementation; commented on databases used to report the hyaluronic acid products; and appreciated the meeting materials being published prior to the public meeting.
 - Vinod Dasa, MD; Gary Myerson, MD; and Phillip Band, MD, Smith & Nephew, stated that hyaluronic acid is more effective than corticosteroids and NSAID; and believes that hyaluronic acid injections maintain function and activity for their population. Requested for the committee to consider coverage as an effective treatment tool for OA of the knee.
 - Johanna Lindsay, The Arthritis Foundation, Pacific Northwest Chapter, stated that based on her experience, the OA population want a quality of life increase for simple daily activities; HA provides this, and individuals with obesity or co-morbidities may not be eligible for surgery; access to HA as an option should be preserved.
 - Jeff Peterson, MD, Washington State Rheumatology Alliance, disagreed with the technology report, based on argument that the use of hyaluronic acid injections are a cost-savings due to decreased surgeries, physical therapy, wheel chairs and time off from work.
- ✓ Open Public Comments: two individuals provided comments during the open portion (limited to three minute comments).
 - Biji Joseph, Genzyme, Manufacturer, commented on how the evidence vendor should have looked at data prior to 2006 and that the Hayes report relied heavily on the effect size.
 - Debra Colfort, Genzyme, Manufacturer, provided a statement regarding the single use of Hyaluronic Acid / Viscosupplementation injection changes the total cost of care which guarantees compliance and minimizes waste.

Agenda Item: Hyaluronic Acid / Viscosupplementation Topic – Agency Data

Dr. Gary Franklin, Department of Labor & Industries, Medical Director, presented to the committee the agency utilization and outcomes for Hyaluronic Acid / Viscosupplementation.

- ✓ Agency Concerns:



- Safety (LOW): adverse events increase with number of treatment courses, generally safe.
- Efficacy (Medium): unknown mechanism, unstudied duration of sub-clinical average result; additive not alternative.
- Cost (High): usage and costs escalating rapidly.
- ✓ Coverage Overview: currently covered by all WA state agencies. DSHS / UMP cover without restrictions. LNI covers when: OA of the knee retards recovery from accepted condition; single course of injections only; and after documented failure of all alternative therapies, including non-pharmacological (e.g. physical therapy), non-opioid analgesics (acetaminophen) and two different NSAID classes.
- ✓ Agency Experience with Products: HA products vary in cost; agency payment data shows: average injection payment range from \$55 to \$164 by product and evidence does not demonstrate superiority or difference in products.
- ✓ Scientific Evidence: Efficacy – despite 50+ trials, no large effect; no consistent clinically meaningful effect; statistically significant pain reduction in some patients. However, study focus on pain reduction in short term – some equivalent to placebo, or NSAIDs; inadequate evidence of functional improvement; inadequate long term studies and follow up; inadequate controls for other treatment; and recent longer (26 weeks) studies have found both exercise and ACS injections superior to Hyaluronic Acid / Viscosupplementation.
- ✓ Utilization Data – Completion of Treatment:

COMBINED AGENCY DATA, 2008

2008 Injection Series	Hyalgan/ Supartz*	Synvisc	Euflexxa	Orthovisc	All Injection Types
Background info					
Total Patients 2008	596	686	163	411	1856
FDA Injection Counts per Procedure	5(3-5)*	3	3	3	
Series Completions					
Patients completing at least 1 series of injections	39%	72%	64%	71%	61%
Patients completing 2 series or more	4%	12%	7%	10%	
Series Incompletions					
Patients who did not complete any injection series	61%	27%	29%	24%	37%
Patients with a single injection only	16%	12%	15%	12%	
Patients with two injections only	11%	15%	15%	12%	
Three injection incomplete series (Hyalgan/Supartz only)	24%				
Four injection incomplete series (Hyalgan/Supartz only)	11%				

*Hyalgan (5 inj) and Supartz (3-5 inj) are combined due to a shared billing code. Completion data may be skewed by the proportion of each drug prescribed, the speed of adoption of FDA approved label changes in practice, and the severity of the patients' condition.

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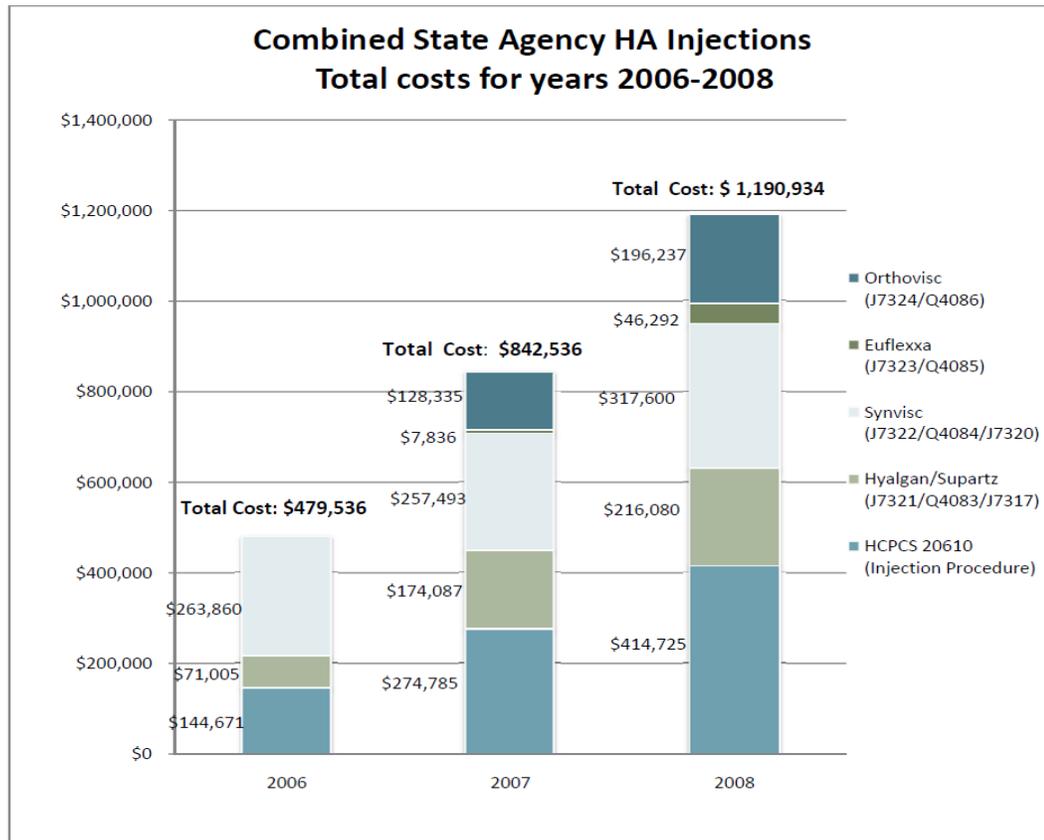


- ✓ FDA inconsistent in injection count approval – Supartz approved for 3, amended to 3 or 5 in 2006 and Orthovisc approved in 2004 for 3 or 4 injections. 8 – 16% of UMP and DSHS patients using Synvisc or Euflexxa (3 injections) receive more injections than FDA approved treatment.
- ✓ Agency Hyaluronic Acid / Viscosupplementation cost experience – average \$838,000 per year, and costs escalating by 40% each year.

UMP, L&I, DSHS DATA 2006-2008

2006-2008	Patient count	Procedure Count	Total Cost
Unified Medical Plan	1969	8424	\$1,201,323
Labor & Industry	934	2917	\$850,330
Dept of Social and Health Services	848	2780	\$461,353
All Agencies	3571	14121	\$2,513,006

- ✓ A Picture of Escalating Costs:



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- ✓ Safety Data: minor adverse events relatively common, increasing in frequency with repeated procedures; adverse events may be elevated with some product types; major adverse events are rare, but do occur; and comparative safety advantage with NSAIDs (systemic) questionable as not used as alternative and relief from Hyaluronic Acid / Viscosupplementation short term.
- ✓ Cost-effectiveness (CE) Evidence: no evidence of clinically significant improvement in outcomes; therefore, cost effective and economic studies are not appropriate. Current cost-effectiveness analysis unclear basis as clinically meaningful improvement not demonstrated; no high quality evidence that treatment is alternative, currently additive; no high quality evidence of number of patients with clinical improvement in pain and function; and assumption on duration of effect is unclear.
- ✓ AMD Recommendations: Non-coverage due to meaningful clinical effect on pain not demonstrated, low evidence on other patient outcomes; harms occur, usually minor, but include serious adverse event (pseudosepsis) and consistent with high quality guidelines weak to negative conclusions.
 - If HTCC finds evidence suggestive of net health benefit, limit to: FDA indications; require evidence of conservative management; limit number of treatment courses and leave product type to agency discretion.

Agenda Item: Evidence Review Presentation

Hayes presented an overview of their evidence report on Hyaluronic Acid / Viscosupplementation for Osteoarthritis (OA) of the Knee.

- ✓ Background – OA: 27 million adults in the U.S.; most commonly affected joint is knee and prevalence is 12 – 16%.
 - Treatment includes: physical therapy, exercise, and/or weight loss
 - Acetaminophen → nonsteroidal anti-inflammatory drugs (NSAIDs) → intraarticular (IA) corticosteroid → total knee replacement (TKR).
- ✓ Background – Hyaluronic Acid / Viscosupplementation: names include hyaluronic acid (HA), hyaluronan sodium hyaluronate. Alternative to NSAIDs, IA corticosteroid. Natural substance in synovial fluid (appears to deplete with OA). FDA approval is for OA of the knee, off-label includes hip, shoulder, ankle, temporomandibular joint, rheumatoid arthritis, and caution of retreatment.
- ✓ Products marketed in the U.S. include: Euflexxa (Ferring); Hyalgan (Sanofi-Aventis); Orthovisc (Anika Therapeutics); Supartz (Seikagaku Corporation) and Synvisc (Genzyme). Different forms of HA: Hylan GF-20 – cross-linked polymer, derivative of HA, high molecular weight; medium molecular weight of HA; and low molecular weight of HA.
- ✓ PICO Methods – Patient Group: Adults with OA of the knee; Intervention(s): Viscosupplementation (hyaluronic acid injection – Hyalgan, Synvisc, Supartz, Orthovisc and Euflexxa); Comparator(s): NSAIDs, corticosteroid injection, physical therapy, oral pain medications, placebo, arthroscopic lavage and/or debridement; Outcome(s): pain, function, quality of life and adverse events.



- ✓ Search Methods – usual MED rapid review process; core sources; literature databases (MEDLINE, Jan 2006 – Dec 2009; systematic reviews (SRs); technology assessments and guidelines. MEDLINE and EMBASE, Sep 2009 – Dec. 2009; primary studies after latest SR search); study design, primary studies – randomized controlled studies (RCTs) only.
- ✓ Search Results:
 - 3 general systematic reviews (SRs) –
 - Hayes Report (2009)
 - AHRQ technology assessment; review of 6 meta-analysis (MAs) plus supplemental analysis (Samson et al., 2007)
 - Cochrane Review with MA (Bellamy et al., 2006)
 - 2 special-issue SRs with MA –
 - Hylan vs. HA (Reichenbach et al., 2007)
 - HA / hylan vs. IA corticosteroid (Bannuru et al., 2009)
 - 4 recent RCTs (late 2009)
 - Various sources of cost / cost-effectiveness data
- ✓ Placebo-Controlled RCTs:

Source	Meta-analysis?	# of placebo-controlled RCTs	SR Quality	RCT Quality
Hayes 2009	No	11	Fair-good	No individual rankings
Samson 2007 (AHRQ)	Yes; reviewed 6 MAs; add'l new analyses	42 (5-32 per MA)	Good (Variable MA quality)	Good (9), fair (16), poor (12), not evaluable (5)
Bellamy 2006 (Cochrane)	Yes (included in Samson 2007)	32	Fair-good	No individual rankings
Altman 2009 Baltzer 2009	N/A; trials from primary lit	2	N/A	Good Good

- ✓ Findings: Efficacy vs. Placebo (moderate-quality evidence; about 50 RCTs, 6 MAs)
 - Statistically significant differences in pain and function, especially during ~1 to 2 months after treatment.



- Benefit may not be clinically important – pooled estimates of difference: < 20 points on 100-point scales (except hylan vs. placebo); standardized effects sizes: 0.0-0.32; 0.80 in 1 MA.
- Conflicting evidence, two 2009 primary RCTs.
- Response rates (2 RCTs): non-significant in ITT analysis (Altman 1998); 76% vs. 62% ($P<0.03$) (Neustadt 2005).

✓ Randomized Comparator Trials:

Comparison	Key Source	# trials	Quality of Source	Quality of Trials
HA vs NSAIDs	Bellamy 2006	6 total; 4 effectiveness and 2 safety	Fair-Good	Not individually assessed,
HA vs IA corticosteroid	Bannuru 2009 (Meta-analysis)	7	Good	Low
Hylan vs non-hylan HA	Reichenbach 2007 (Meta-analysis)	13	Good	Generally poor or incomplete reporting
HA vs conventional treatment	Hayes 2009	2 (Raynauld 2002; Kahan 2003)	Fair-Good	Not individually assessed.

- ✓ Findings: HA vs. Other Treatments (Low Quality Evidence) –
 - Improvement comparable with NSAIDs (4 RCTs), fewer adverse events (2 RCTs).
 - Longer-lasting benefit than IA corticosteroids (1 MA of 7 RCTs) – HA superior after first few weeks; largest effect size 0.39 (95% CI, 0.18-0.59), 17 – 26 weeks.
 - Response rates (2 RCTs) – 62% vs. 35% ($P=0.0001$), ITT analysis; 65% vs. 40% ($P=0.0001$), ITT analysis.
- ✓ Findings: Effectiveness by Products (Low Quality Evidence) – Hylan may have superior benefit over non-cross linked HA; magnitude unlikely to be clinically important (1 MA of 13 comparator trials); no evidence of difference, low vs. medium molecular weight (2 MAs of placebo-controlled trials).
- ✓ Findings: Safety – best estimate* (*estimate available only from studies of hylan) is 2% (per injection) risk of local, transient reactions, serious reactions possible; HA vs. placebo = similar; HA vs. corticosteroid = unavailable; Hylan vs. non-hylan HA = small absolute increase in overall risk; and increasing risk with repeat courses of treatment* (*evidence available only from studies of hylan).
- ✓ Findings: Effectiveness by Subpopulation (Low Quality Evidence) – disease severity = conflicting evidence; age, individual trials = conflicting evidence; age, analysis of 20 trials = younger age, greater efficacy (vs. placebo); race/ethnicity, gender, primary vs. secondary OA, disease duration, weight, prior treatments = Not studied or 1 or 2 studies showed no relationship.



- ✓ Findings: Cost Implications -- \$65 to \$195 per injection (U.S. estimate); no cost-effectiveness conclusions: 2 randomized trials suggest acceptable cost effectiveness (Canada, France); Celecoxib more cost-effective than HA as an alternative to naproxen in patients who have declined TKR (Taiwan); unknown representativeness of effectiveness estimates; and may not apply to U.S.
- ✓ Guidelines: 3 high-quality guidelines –
 - Weakly positive in favor of HA (OARSI); no recommendation because of unclear clinical importance of benefit (AAOS); and negative because of limited cost-effectiveness analysis (NICE).
 - 3 poor-quality guidelines: Clinical option
- ✓ Limitations of the Evidence: Poorer-quality and smaller trials may have inflated estimates of efficacy; variation in study methods; few data on response rates, comparative effectiveness, and subpopulations; no safety data from large databases, except for hylan; no analysis of synergistic effects; and no U.S. economic evaluations.
- ✓ General Conclusion: On average, improvement in pain and function (most relief during 1-2 months after treatment). Magnitude of benefit may be too small to be clinically important. Safety risks small, generally non-serious.
- ✓ Practice Considerations: Longer-lasting benefit compared with intraarticular corticosteroids (low quality evidence). Potential alternative to NSAIDs after simpler treatments have failed or next step after NSAIDs have failed (assumed role in cost-effectiveness studies; sparse evidence). Ability to avert total knee replacement has not been studied.

Agenda Item: HTCC Hyaluronic Acid / Viscosupplementation Discussion and Findings

Brian Budenholzer, Committee Chair, led a discussion of the evidence related to the safety, efficacy, and cost effectiveness of Hyaluronic Acid / Viscosupplementation beginning with identification of key factors and health outcomes, and then a discussion of what evidence existed on those factors.

1. Evidence availability and technology features

- 1.1 The evidence based technology assessment report indicates that 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.
- 1.2 The evidence based technology assessment report indicates that 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.



- 1.3 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.
- 1.4 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).
- 1.5 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).
- 1.6 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).
- 1.7 The evidence based technology assessment report identified 6 expert treatment guidelines and no national Medicare policy relating to hyaluronic acid.
- 1.8 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. Evidence about the technology's safety

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.

- 2.1 The evidence based technology assessment report indicates that 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.
- 2.2 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.
- 2.3 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%).
- 2.4 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. Evidence about the technology's efficacy and effectiveness

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.

- 3.1 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.
- 3.2 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).
- 3.3 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.
- 3.4 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.
- 3.5 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.
- 3.6 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

- 4.1 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
- 4.2 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.
- 4.3 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.

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5. Evidence about the technology's value and cost-effectiveness

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.

- 5.1 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.
- 5.2 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).
- 5.3 Washington State Agency utilization and cost information indicated rising utilization; annual costs at \$1.2 million and per treatment cost of \$665.00.
- 5.4 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.
- 5.5 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.
- 5.6 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. Evidence on Medicare Decision and Expert guidelines

Committee reviewed and discussed the expert guidelines as identified and reported in the technology assessment report.

- 6.1 Centers for Medicare and Medicaid Services – no national Medicare coverage policy.

- 6.2 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).
- 6.3 Three guidelines rated high quality based on modified AGREE international checklist for evidence based guidelines are summarized::
- (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.
 - (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.
- 6.4 Three guidelines rated low quality based on modified AGREE international checklist for evidence based guidelines supported use of OA for knee pain.

Committee Conclusions

Having made findings as to the most significant and relevant evidence regarding health outcomes, key factors and identified evidence related to those factors, primarily based on the evidence based technology assessment report, the committee concludes:

1. Evidence availability and technology features

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

- 1.1. Osteoarthritis (OA) is the most common form of chronic articular disease. The most commonly affected joint is the knee. To date, neither a known cure for OA nor a disease-modifying agent is available. Therefore, treatment is focused on reducing pain, maintaining and/or improving joint mobility, and limiting functional impairment.
- 1.2. 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.

2. Is it safe?

The committee concludes that the comprehensive evidence indicates that hyaluronic acid / viscosupplementation is equally safe to alternative treatments. Key factors to the committee's conclusion included:

- 2.1. The committee agreed that there are not mortality concerns.
- 2.2. In terms of morbidity, the committee agreed with the evidence report that serious complications were rare and minor complications included local reaction.



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- 2.3. The committee agreed that the HA injection harms (mostly local) were comparable or less harmful than the systemic effects of NSAIDs, but that evidence was lacking that HA injections are a demonstrated alternative to NSAIDs.

3. Is it effective?

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.

- 3.1. Overall, the committee agreed with the evidence based report that there is moderate quality evidence of a consistent pain relief benefit of HA over placebo based on over 50 RCTs. While there is an impressive body of evidence, some committee members struggled with the limitations of the studies and were troubled that despite a decade of research and the number of trials; the number of patients and magnitude and duration of pain relief benefit are still uncertain, as well as the limited study on other important outcomes.
- 3.2. A well done, more recent RCT validated previous findings (Altman 2009); mean effect size of 6.6% at 26 weeks; patients with great than 20% improvement odds ratio of 1.7 (58% HA arm clinical improvement and 46% placebo arm clinical improvement) was convincing to many committee members.
- 3.3. The evidence does not permit conclusions on length of time for pain relief, though it appears to be a delayed effect of several weeks and several low quality trials demonstrate benefit beyond corticosteroid injections (2 to 6 months).
- 3.4. Functional status was less well studied and/or reported, but trended similar to pain reduction in over 15 studies with validated instruments (WOMAC and Lequesne).
- 3.5. No reliable information was available on important patient oriented outcomes of reduction in analgesic medication, quality of life, or delay in surgical intervention.
- 3.6. While promoted as an alternative, there is very little evidence that HA is an alternative rather than additional treatment, and the committee evaluated the technology as an additional option.

4. Evidence about the technology's special populations, patient characteristics and adjunct treatment

The committee agreed that no compelling evidence exists to differentiate sub groups or special populations.

- 4.1. The committee agreed with the evidence based report that there is inadequate evidence to identify characteristics that either enhance or reduce the efficacy of HA such as age, race/ethnicity, gender, primary vs. secondary, BMI weight, disease severity and duration; prior treatments).
- 4.2. Specifically with respect to the difference in products and protocols, the committee concluded that there is insufficient data to demonstrate that any one product or administration protocol is superior.

5. Is it cost-effective?

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.

- 5.1. The evidence report adequately summarized the poor cost evidence based primarily on the inability to evaluate the representativeness of the study models: short time-frames; the full

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- economic evaluations were not conducted in the United States; no cost data on specific single-injection treatments; assumptions about delay of total knee replacement surgery; and no cost-effectiveness analysis of HA versus intraarticular corticosteroid injection.
- 5.2. Committee acknowledged the state agency costs of hyaluronic acid / viscosupplementation treatment injections were nearly \$2.5 million over three years; have risen steadily over past three years; to about \$1.2 million per year. Current per series costs are about \$670 to state.
 - 5.3. Committee reviewed QALY from several (albeit low quality studies) in the \$10,000 CAD to \$50,000 range; noting this is well below any common QALY standard and that the treatment is relatively inexpensive.

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 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 Coverage Vote

The clinical committee utilized their decision tool to first gauge committee judgment on the status of the evidence in the three primary areas of safety, efficacy, and cost.

Hyaluronic Acid / Viscosupplementation Evidentiary Votes:

Is there sufficient evidence under some or all situations that Hyaluronic Acid / Viscosupplementation for the treatment of Osteoarthritis of the knee is:

	Unproven (no)	Equivalent (yes)	Less (yes)	More (yes)
Effective	3	1	0	6
Safe	0	10	0	0
Cost-effective Overall	7	0	1	2

Hyaluronic Acid / Viscosupplementation vote: Based on the evidence provided and the information and comments presented, the committee moved to a vote on coverage.

HTCC COMMITTEE COVERAGE DETERMINATION			
	Not covered	Covered Unconditionally	Covered Under Certain Conditions
Hyaluronic Acid / Viscosupplementation	3	0	7

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Outcome: The committee chair directed HTA staff to prepare a Findings and Decision document on Hyaluronic Acid / Viscosupplementation reflective of the majority vote for final approval at the next public meeting.

- 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:
 1. In patients who have not had an adequate response to nonpharmacological conservative treatment and simple analgesics;
 2. Is limited to two courses per year with at least four months between courses; and
 3. 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.