HEALTH EVIDENCE REVIEW COMMISSION (HERC) COVERAGE GUIDANCE: VISCOSUPPLEMENTATION FOR OSTEOARTHRITIS OF THE KNEE

Initial HERC approval 10/11/2012
Reaffirmed 11/13/2014

This coverage guidance was created under HERC's 2012 coverage guidance process and does not include strength of recommendation, a GRADE-informed framework or coverage guidance development framework.

As a part of the normal evidence review process, the Health Technology Assessment Subcommittee reviewed new evidence in September, 2014 (see Appendix A). Two reviews and one guideline were identified in the trusted sources.

HERC Coverage Guidance

Viscosupplementation should not be covered for the treatment of pain associated with Osteoarthritis (OA) of the knee.

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

Hayes, Inc. (2010). *Hyaluronic Acid/Viscosupplementation.* Produced for the Medicaid Evidence-based Decisions Project and the Washington Health Technology Assessment Program. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science

University. Retrieved September 10, 2012, from http://www.hta.hca.wa.gov/documents/ha_final_report_042610.pdf

Hayes, Inc. (2010). *Viscosupplementation for osteoarthritis of the knee.* Produced for the Medicaid Evidence-based Decisions Project. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University. Retrieved September 10, 2012, from http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/med/index.cfm

Samson, D. J., Grant, M. D., Ratko, T. A., Bonnell, C. J., Ziegler, K. M., & Aronson, N. (2007). *Treatment of primary and secondary osteoarthritis of the knee.* AHRQ Evidence Report/Technology Assessment No. 157. AHRQ Publication No. 107-E012. Evidence Report/Technology Assessment, (157), 1-157. Retrieved September 10, 2012, from http://www.ncbi.nlm.nih.gov/books/NBK38385/

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

CLINICAL BACKGROUND

Osteoarthritis (OA) is the most common form of chronic articular disease, affecting 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 improvement from medical therapy. Pharmacological therapy generally begins with acetaminophen, followed by nonsteroidal anti-inflammatory drugs (NSAIDs) if sufficient pain relief is not obtained. There is a small risk of systemic adverse effects with NSAIDs. Aspiration of fluid followed by intraarticular injection of a corticosteroid ameliorates pain in some patients, but duration of relief is usually limited to one to three weeks. Additionally, repeated intraarticular injections of corticosteroids have the potential to cause postinjection flare, infection, and progressive, long-term cartilage damage.

Recently, 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). Hyaluronic acid 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. Five HA products are currently marketed in the United States: Euflexxa® (Ferring), Hyalgan® (Sanofi-Aventis), Orthovisc® (Anika Therapeutics), Supartz® (Seikagaku Corporation), and Synvisc® (Genzyme). Synvisc is a derivative of HA that consists of cross-linked polymers; the compound

is referred to as Hylan G-F 20. 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. Recent systematic reviews have come to contradictory conclusions regarding the effectiveness of viscosupplementation, and national guidelines vary in their recommendations.

EVIDENCE REVIEW

There is consistent evidence demonstrating that viscosupplementation results in lower mean pain scores and improves mean function scores a few weeks after treatment. However, the magnitude of benefit may be too small to be clinically important. This evidence is derived from a quantitative synthesis of six meta-analyses performed by the Agency for Healthcare Research and Quality in 2007 which included 42 randomized placebo controlled trials and over 5000 patients (Samson 2007). The authors found that the average change in pain score, although consistent and statistically significant, was small, with weighted mean differences in the range of 1.0 to 22.5 on a 100 point visual acuity scale. While there is no definitive definition of clinical significance, several authors, including Sampson, consider a 20 to 40 point improvement on 100 point pain scales to be clinically significant. The authors also reviewed the five previously published study-level meta-analyses that came to a variety of conclusions regarding the efficacy of viscosupplementation. These ranged from negative to moderately positive to strongly positive. The authors of the Samson review considered only one meta-analysis to have reported data and analysis that fully supported the meta-analysis authors' conclusion. This was also the metaanalysis with a negative conclusion—that the *clinical* effectiveness of viscosupplementation has not been proven and that viscosupplementation may be associated with a higher risk of adverse events.

There is a much greater volume of evidence regarding impact on pain than on function, and many studies did not follow patients beyond three months. Therefore, the impact of viscosupplementation on eventual recovery of function is uncertain. Compared with intraarticular corticosteroid injection, viscosupplementation appears to confer longer-lasting benefit, but the evidence was considered low quality. For comparisons with other treatments, there was insufficient evidence to allow any conclusion. Adverse events occur at a frequency of approximately 2% in single courses of treatment and are primarily transient local reactions, although rare, serious reactions are possible. The rate of adverse events per patient has been shown to increase with repeat courses of treatment, but the only available data were for hylan (high-molecular weight HA).

Evidence pertaining to issues other than efficacy and safety is of low quality:

- Available evidence suggests that viscosupplementation may be as effective as NSAIDs (four RCTs) and results in fewer systemic adverse events (two RCTs); in comparison with intraarticular corticosteroids, it has a delayed onset and longer lasting benefit (nine RCTs plus meta-analysis).

- Hylan may have a superior benefit compared with that of non–cross-linked HA, but the magnitude of difference is very uncertain and hylan poses a small increase in the risk of adverse events.
- To date, there is no evidence of a difference in benefit between low and medium molecular weight HA.
- Younger age may be associated with greater efficacy; evidence pertaining to effectiveness by other patient characteristics and history is lacking.

OVERALL SUMMARY

While the evidence demonstrates that viscosupplementation results in lower mean pain scores and improved mean function scores a few weeks after treatment, the magnitude of benefit may be too small to be clinically important.

PROCEDURE

Viscosupplementation

DIAGNOSES

Osteoarthritis of the knee

APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
715	Osteoarthrosis and allied disorders Note: Localized, in the subcategories below, includes bilateral involvement of the same site. Includes: arthritis or polyarthritis: degenerative hypertrophic degenerative joint disease osteoarthritis
715.16	Osteoarthrosis localized primary involving lower leg
715.26	Osteoarthrosis localized secondary involving lower leg
715.36	Osteoarthrosis localized not specified whether primary or secondary involving lower leg
715.96	Osteoarthrosis unspecified whether generalized or localized involving lower leg
717	Internal derangement of knee Includes: degeneration of articular cartilage or meniscus of knee; rupture, old of articular cartilage or meniscus of knee; tear, old of articular cartilage or meniscus of knee
ICD-9 Volume 3 (Procedure Codes)	
81.92	Injection of therapeutic substance into joint or ligament as an ICD-9 procedure
ICD-10 Diagnosis Codes	
M15	Polyarthrosis Includes: arthrosis with mention of more than one site Excludes: bilateral involvement of single joint (M16-M19)
M15.0	Primary generalized (osteo)arthrosis
M15.3	Secondary multiple arthrosis
M15.4	Erosive (osteo)arthrosis
M15.8	Other polyarthrosis
M15.9	Polyarthrosis, unspecified
M17	Gonarthrosis (arthrosis of knee)
M17.0	Primary gonarthrosis, bilateral
M17.1	Other primary gonarthrosis
M17.2	Post-traumatic gonarthrosis, bilateral
M17.3	Other post-traumatic gonarthrosis
M17.4	Other secondary gonarthrosis, bilateral
M17.5	Other secondary gonarthrosis
M17.9	Gonarthrosis, unspecified
M19	Other arthrosis
CPT Codes applicable to viscosupplementation	
20610	Arthrocentesis, aspiration, and/or injection; major joint or bursa (e.g. shoulder, hip, knee joint)
CPT Codes applicable to total knee replacement (TKR)	
27440	Arthroplasty, knee tibial plateau

CODES	DESCRIPTION
27441	Arthroplasty, knee tibial plateau; with debridement and partial synovectomy
27442	Arthroplasty, femoral condyles, or tibial plateau(s) knee
27443	Arthroplasty, femoral condyles, or tibial plateau(s) knee; with debridement and partial synovectomy
27445	Arthroplasty, knee, hinge prosthesis (e.g., Walldius type)
27446	Arthroplasty, knee condyle and plateau; medial or lateral compartment
27437	Arthroplasty, patella; without prosthesis
27438	Arthroplasty, patella; with prosthesis
27447	Arthroplasty, knee condyle and plateau; medial and lateral compartments with or without patella resurfacing (total knee arthroplasty)
HCPCS Level II Codes for viscosupplementation	
J7321	Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose
J7323	Hyaluronan or derivative, Euflexxa, for intraarticular injection, per dose
J7324	Hyaluronan or derivative, Orthovisc, for intraarticular injection
J7325	Hyaluronan or derivative, Synvisc or Synvisc-One, for intraarticular injection, 1 mg
HCPCS Level II Codes for intraarticular cortisone injection	
J0702	Injection betamethasone acetate 3 mg and betamethasone sodium phosphate, 3 mg
J0704	Injection, betamethasone sodium phosphate per 4 mg
J1020	Injection, methylprednisone acetate, 20 mg
J1030	Injection, methylprednisone acetate, 40 mg
J1040	Injection, methylprednisone acetate, 80 mg
J1094	Injection, dexamethasone acetate, 1 mg
J1100	Injection, dexamethasone sodium phosphate, 1 mg
J1700	Injection, hydrocortisone acetate, up to 25 mg
J1710	Injection, hydrocortisone sodium phosphate, up to 50 mg
J1720	Injection, hydrocortisone sodium succinate, up to 100 mg
J2650	Injection, prednisolone acetate, up to 1 mL
J2920	Injection methylprednisone sodium succinate up to 40 mg
J2930	Injection methylprednisone sodium succinate up to 125 mg
J3302	Injection triamcinolone diacetate, per 5 mg
J3303	Injection triamcinolone hexacetonide, per 5 mg

Note: Inclusion on this list does not guarantee coverage

APPENDIX A

SCANNING RESULTS

Two reviews and one guideline pertaining to OA of the knee were identified in the core sources that were published after the date of the MED report. In addition, an AHRQ report is in progress, and a Hayes report addressed post-operative viscosupplementation for a variety of knee conditions. Summary results and/or conclusions of the two completed reviews and the guideline are presented below.

Canadian Agency for Drugs and Technologies in Health (CADTH). (2014). ***Viscosupplementation for the Treatment of Osteoarthritis of the Knee: Clinical Effectiveness and Guidelines*****. Ottawa, CA: CADTH. Retrieved from http://www.cadth.ca/media/pdf/htis/mar-2014/RB0647%20Viscosupplementation%20for%20Knee%20OA%20Final.pdf**

CONCLUSION

Of the nine systematic reviews (SR) identified, five SRs indicated some benefit regarding the use of intra-articular hyaluronic acid (IAHA) for the treatment of knee osteoarthritis (OA), whereas the other four SRs did not identify any benefit. In the SRs identifying benefits, IAHA was noted to be most efficacious around eight weeks. Prolonged effects of IAHA were observed in studies that compared it to other active treatments, particularly intra-articular corticosteroid injections. In the SRs that observed no benefits of IAHA for knee OA, one highlighted a particularly large placebo effect which appeared to skew the IAHA effectiveness, while another noted that probable industry bias swayed results in favour of IAHA. The other two SRs observed no clinical benefit; however, it was proposed that IAHA could be an alternative to non-steroidal anti-inflammatory drugs in older populations at risk for adverse events, due to its comparable favourable safety profile.

Three of the identified guidelines do not recommend IAHA for the treatment of knee OA10- and another does not include any conclusive recommendations. Of the four guidelines that recommend IAHA use for knee OA, one conditionally recommends IAHA for patients with inadequate response to initial therapy, another recommends IAHA use for moderate to severe knee OA (noting this was based on consensus only), and the other two guidelines provide algorithms for IAHA use.

Rutjes, A. W., Jüni, P., da Costa, B. R., Trelle, S., Nüesch, E., & Reichenbach, S. (2012). Viscosupplementation for Osteoarthritis of the KneeA Systematic Review and Meta-analysis. ***Annals of internal medicine, 157*****(3), 180-191. http://eds.b.ebscohost.com/ehost/pdfviewer/pdfviewer?vid=4&sid=daad4ec3-c5c4-41d9-b425-6257dfbd50ff%40sessionmgr114&hid=106**

MAIN RESULTS

Eighty-nine trials involving 12,667 adults met inclusion criteria. Sixty-eight had a sham control, 40 had a follow-up duration greater than 3 months, and 22 used cross-linked forms of hyaluronic add. Overall, 71 trials (9617 patients) showed that viscosupplementation moderately reduced pain (effect size, -0.37 [95% CI, -0.46 to -0.28]). There was important between-trial heterogeneity and an asymmetrical funnel plot: Trial size, blinded outcome assessment, and publication status were associated with effect size. Five unpublished trials (1149 patients) showed an effect size of -0.03 (CI, -0.14 to 0.09). Eighteen large trials with blinded outcome assessment (5094 patients) showed a clinically irrelevant effect size of -0.11 (CI, -0.18 to -0.04). Six trials (811 patients) showed that viscosupplementation increased, although not statistically significantly, the risk for flare-ups (relative risk, 1.51 [CI, 0.84 to 2.72]). Fourteen trials (3667 patients) showed that viscosupplementation increased the risk for serious adverse events (relative risk, 1.41 [CI, 1.02 to 1.97]).

LIMITATIONS

Trial quality was generally low. Safety data were often not reported.

CONCLUSION

In patients with knee osteoarthritis, viscosupplementation is associated with a small and clinically irrelevant benefit and an increased risk for serious adverse events.

Department of Veterans Affairs/Department of Defense (VA/DoD).(2014). *Clinical practice guideline for the non-surgical management of hip & knee osteoarthritis*. Washington, D.C.: VA/DoD. Retrieved from http://www.healthquality.va.gov/guidelines/CD/OA/VADoDOACPGFINAL090214.pdf

RECOMMENDATIONS

For patients with symptomatic osteoarthritis of the knee, clinicians may consider intra-articular corticosteroid injection. [C]

There is insufficient evidence to recommend for or against the use of intra-articular hyaluronate/hylan injection in patients with OA of the knee; however it may be considered for patients who have not responded adequately to non-pharmacologic measures and who have an inadequate response, intolerable adverse events, or contraindications to other pharmacologic therapies. [I]

SUMMARY

Although the evidence is somewhat mixed, it does not appear to be substantially different from when the current coverage guidance recommendations were made. In addition, another review

is currently in progress, it may be reasonable to consider updating this guidance once it has been completed.