Medical Drug Clinical Criteria

Subject:	Hyaluronan Injections		
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Overview

This document addresses the use of hyaluronan injections for the replacement or supplementation of naturally occurring intra-articular lubricants in individuals with musculoskeletal conditions. This therapy may also be referred to as viscosupplementation.

Osteoarthritis is a degenerative condition of the joints and is the most common form of arthritis. Osteoarthritis commonly affects the hands and the weight-bearing joints including the knees, hips, feet and spine. Afflicted joints experience loss of synovial fluid, a protective substance which aids in absorbing shock and lubrication in the joints. Low synovial fluid levels and other mechanisms cause a progressive breakdown of the cartilage lining the ends of bones that are necessary for proper cushioning and smooth function of joints. Because of this breakdown of cartilage, bones rub against each other causing pain, loss of movement and further destruction of the joint. The severity of osteoarthritis can range from very mild to very severe. There is no cure for osteoarthritis and current treatment focuses on relieving symptoms and improving function. The hyaluronan injections are considered to be a device by the United States Food and Drug Administration and several have been approved via the premarket approval process.

Proposed use of hyaluronan for osteoarthritis of the knee is derived from demonstration of benefit of varying degrees in a number of trials and meta-analyses of randomized trials. However, many analyses have not shown a clinical benefit beyond the effect seen with placebo. Evidence from recent large double-blinded high-quality trials suggests the clinical benefit of hyaluronan is of minimal benefit over intra-articular placebo (Bannuru 2015). Intra-articular hyaluronan may be associated with potential side effects including pain flare-ups and joint infection, and the use of hyaluronan remains controversial in clinical practice.

In a 2014 study by van der Weegen and colleagues, the authors evaluated the effectiveness and safety of hyaluronic acid compared to placebo. This was a double-blind, placebo-controlled study in which 196 participants with osteoarthritis of the knee received either hyaluronic acid injections (n=99) or saline placebo injections (n=97). Participants received three weekly injections and were followed for 6 months. Efficacy was evaluated using 100-mm visual analog scores (VAS) and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score and recording of limitations in sports and work activities. Both treatment groups showed an improvement in pain and functional scores from baseline to 6 months follow-up. Pain during 50 m walking improved from 56.4 to 38.1 for the hyaluronic acid group and from 58.2 to 39.6 in the placebo group. WOMAC scores improved from 39.0 to 29.3 points for the hyaluronic acid group and from 40.8 to 28.8 points in the placebo group. While symptoms and function improved from baseline, neither treatment group showed a significant difference in any outcome at any follow-up time.

In a 2016 study by Tammachote and colleagues, the authors evaluated the efficacy of a single injection of hylan G-F 20 and triamcinolone acetonide for relieving pain and improving function in participants with osteoarthritis of the knee. In this prospective, double-blind, randomized controlled trial, 99 participants were randomized to either hylan G-F 20 (n=50) or triamcinolone acetonide (n=49). With a follow-up period of 6-months, primary outcome measures included knee pain, functional improvement and knee range of motion. Knee pain was analyzed using a 100-mm VAS. Knee function was measured using 3 dimensions of the modified WOMAC. Range of motion of the knee was measured with a goniometer. In evaluation of pain relief, the triamcinolone acetonide group had better overall pain improvement in the first week after injection. The participants in both groups showed pain relief after injections that lasted up to 6 months. At 6 months, the mean change in VAS was -29 points (95% confidence interval [CI], -36.4 to -22.7 points) in the hylan G-F 20 group and -30 points (95% CI, -36.0 to -22.8 points) in the triamcinolone acetonide group ($p<0.0001$). Both treatment groups had similar overall change in the mean modified WOMAC scores. Two weeks after injection, the triamcinolone acetonide group had better mean functional improvement compared to the hylan G-F 20 group. At the end of 6 months, the mean modified WOMAC scores improved from 43 to 21 points (95% CI, 16.7 to 29.2 points) in the hylan G-F 20 group and from 39 to 21 points (95% CI, 11.0 to 24.3 points) in the triamcinolone acetonide group. Range of motion of the knee was not different between the two treatment groups at any time during the study. After 6 months, those treated with hylan G-F 20 improved mean knee flexion by 6° and those treated with triamcinolone acetonide improved mean knee flexion by 8°. This study is limited by the lack of a placebo group, however, the authors note that “both corticosteroid and hyaluronic acid injections have superior efficacy compared with a placebo injection.”
In 2015 meta-analysis, Bannuru and colleagues reported on the efficacy of treatments for osteoarthritis of the knee evaluating pain, function and stiffness. A total of 137 studies made up of 33,243 participants were included in the analysis. Inclusion criteria into the

analysis included randomized controlled trials that compared at least two interventions (acetaminophen, diclofenac, ibuprofen, naproxen, celecoxib, intra-articular corticosteroids, intra-articular hyaluronic acid, oral placebo and intra-articular placebo). Pain-related outcomes were analyzed in 129 trials. In these trials, all of the interventions were better than oral placebo, reporting that intra-articular placebo was better than oral placebo. Physical function outcomes were analyzed in 76 trials. All interventions except for intra-articular corticosteroids were superior to oral placebo. A total of 55 trials were analyzed for stiffness outcomes. Intra-articular hyaluronic acid was reported to be better than intra-articular placebo; however, intra-articular placebo was not better than oral placebo. The authors concluded that all treatments except for acetaminophen showed significant pain improvement and intra-articular treatments were more effective than the non-steroidal anti-inflammatory drugs (NSAIDS), noting that the effect of hyaluronic acid injection seems to derive from the use of intra-articular delivery.

A 2015 meta-analysis by Richette and colleagues analyzed 8 randomized controlled trials which investigated intra-articular hyaluronic acid injections for osteoarthritis of the knee. The studies compared hyaluronic acid injection to a placebo saline injection. The primary outcome was the intensity of pain (using VAS) and secondary outcome was knee function at 3 months. For pain intensity, the standardized mean difference was −0.21 (95% CI −0.32 to −0.10) favoring intra-articular hyaluronic acid injection. Five of the trials had information about functional outcomes with a standardized mean difference of −0.12 (95% CI −0.22 to −0.02). Limitations to this meta-analysis are potential for publication bias since only published trials were included, a short follow-up time of 3 months and the studies did not separately distinguish the different types of hyaluronic acid, only assessing hyaluronic acid as a whole.

In 2015, Campbell and colleagues performed a systematic review of overlapping meta-analyses comparing different treatment of knee osteoarthritis to intra-articular hyaluronic acid. The purpose was to determine which meta-analyses provided the best current evidence and identify potential causes of disagreement. The included studies had varied levels of evidence ranging from level I to level IV. All of the included studies compared the use of intra-articular hyaluronic acid to oral NSAIDS, intra-articular corticosteroids, intra-articular platelet-rich plasma or intra-articular placebo. A total of 14 meta-analyses were included in the review with 4 of the 14 having industry funding. Of the 10 studies that looked at the effects of intra-articular hyaluronic acid versus intra-articular placebo, 5 found an improvement in pain and 4 found an improvement in function. However, 3 meta-analyses found no difference between hyaluronic acid and placebo in terms of pain and 4 studies found no difference in function. There were 3 studies which examined the efficacy of intra-articular hyaluronic acid to oral NSAIDS; none of these studies showed clinically relevant differences between the two treatments. In the studies which compared intra-articular hyaluronic acid injections to intra-articular corticosteroid injections, the corticosteroids initially provided better relief of pain 4 weeks following the injection, but the intra-articular hyaluronic acid showed more positive effects 5-13 weeks following injections. Both intra-articular hyaluronic acid injection and intra-articular platelet-rich plasma showed improvements in knee function at 2 and 6 months following injection, the effects of the intra-articular platelet-rich plasma were more robust. In the studies which compared different formulations of hyaluronic acid products, no definitive conclusions could be made about the best product. The authors note that because of the high prevalence of osteoarthritis of the knee, many clinical trials, systematic reviews and meta-analyses have been conducted in an attempt to determine the best non-operative treatment, “however, a clear gold standard has not been identified.” As noted by the authors, the quality of the systematic review is limited by the quality of the studies included in the review, including methodological limitations inherent to those studies.

Bhandari and colleagues (2017) published a review of 8 meta-analyses on intra-articular hyaluronic acid therapy for mild-to-moderate knee osteoarthritis. The meta-analyses included were published within 5 years of the review, only included randomized control trials, and evaluated the effects of intra-articular hyaluronic acid therapy compared with intra-articular placebo or non-interventional controls for knee osteoarthritis. While the authors found statistically significant improvements in pain, function and stiffness outcomes for hyaluronic therapy compared with placebo or nonintervention in meta-analyses considered, the analysis did not address questions surrounding clinical significance. In addition, many of the underlying studies used in the reviewed meta-analyses included methodological limitations such as insufficient blinding, non-uniform methodology, small study samples, and inappropriate or no control group, as well as potential for publication bias.

Other authors have also published literature reviews regarding the use of hyaluronan injections for the treatment of osteoarthritis of the knee (Jevsevar 2015; Nguyen 2016). The positive results are inconsistent, and supportive meta-analyses are limited by wide-heterogeneity of the published literature (including insufficient blinding, non-uniform methodology, small study samples and inappropriate or no control group), as well as potential for publication bias. Many analyses have not shown benefit beyond the effect seen with placebo, and the treatment effect demonstrated in positive analyses is often of questionable clinical significance. In reviewing the issue of clinical significance, demonstration of a clinically meaningful difference is mixed among meta-analyses, and in many publications, clinical importance is only achieved when the full therapeutic effect of hyaluronan is considered; that is, factoring in the placebo effect attributed to intra-articular administration.

In 2019, the American College of Rheumatology (ACR) published updated guidelines for the management of osteoarthritis of the hand, hip and knee (Kolasinski 2019). The guidelines conditionally recommend against intraarticular hyaluronic acid injections in individuals with knee osteoarthritis. ACR states hyaluronic acid injection benefit has been primarily found in studies with higher risk of bias. The current guidance is based on a systemic review limited to trials with low risk of bias. This meta-analysis has shown the effect size of hyaluronic acid injections compared to saline injections approaches zero.

The American Academy of Orthopedic Surgeons (AAOS) published their Clinical Practice Guideline for Treatment of Osteoarthritis of the Knee in 2013. In their recommendations, the AAOS states that they "cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee." It was noted that the recommendation was based on lack of efficacy, not on potential harm. In their 2021 Management of Osteoarthritis of the Knee (Non-Arthroplasty) guideline update, AAOS revised their recommendation to state hyaluronic acid intraarticular injection is not recommended for routine use in the treatment of symptomatic osteoarthritis of the knee. The updated review of the evidence found that statistically significant improvements were associated with high-molecular cross-linked hyaluronic acid but when compared to mid-range molecular weight, statistical significance was not maintained. This newer analysis did not demonstrate clinically relevant differences when compared to controls.

In 2019, Osteoarthritis Research Society International (OARSI) published updated guidelines for the non-surgical management of knee, hip and polyarticular osteoarthritis (Bannuru 2019). In the 2014 guidance, intra-articular hyaluronic acid was listed as a treatment of "uncertain appropriateness." The 2019 guidance updated intra-articular hyaluronic acid to conditionally recommended (low consensus) for knee osteoarthritis for longer-term treatment effect (symptom improvement beyond 12 weeks) and favorable safety profile. Treatment modalities with a strong recommendation for knee osteoarthritis include arthritis education, structured land-based exercise programs and topical NSAIDs.
The American Medical Society for Sport Medicine (AMSSM) published a consensus statement in 2016 recommending the use of hyaluronic acid for the appropriate individuals with knee osteoarthritis. The recommendation is based on network meta-analysis of 11 articles showing a small but statistically significant improvement for participants treated with hyaluronic acid compared to those treated with intra-articular corticosteroids or placebo. Potential for bias was present among the majority of studies included in the meta-analysis, including incomplete data reporting, selective reporting or the absence of blinding of participants and personnel.

In 2017, a workgroup of clinicians published Appropriate Use Criteria (utilizing existing literature supplemented with expert opinion) for use of hyaluronic acid in the treatment of osteoarthritis of the knee (Bhadra and colleagues). The authors found that hyaluronic acid is appropriate for 6 of 17 described clinical scenarios – namely individuals with mild to moderate disease, including those who have experienced an incomplete response or have failed other therapies. The authors concede that evidence on hyaluronic acid is limited – that when compared with active treatments, effects are smaller or there are no clear differences. While the authors conclude that hyaluronic acid injections play a positive role in the treatment of knee OA, they also note that additional research is needed.

In conclusion, there is debate on the effectiveness of hyaluronan injections for treatment of osteoarthritis of the knee. There is a lack of consensus on the ideal treatment regimen regarding the number of injections and the interval between injections as well as the use of repeated treatment cycles making it difficult to establish effectiveness of hyaluronan. There are also differences in available hyaluronan products including source, molecular weight, concentration and volume. With differing protocols for the treatment of osteoarthritis of the knee with hyaluronan injections, different dosages, different formulations and the timing of injections not being uniform and varying across trials, it is difficult to assess the overall treatment effect of hyaluronan for osteoarthritis of the knee.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Hyaluronan Injections

Requests for hyaluronan injections for all joints including but not limited to the knee, ankle, shoulder, hip, temporomandibular joint, or thumb may not be approved.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS	
J7318	Hyaluronan or derivative, Durolane, for intra-articular injection, per dose
J7320	Hyaluronan or derivative, GenVisc 850, for intra-articular injection, 1 mg
J7321	Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose
J7322	Hyaluronan or derivative, Hymovis, for intra-articular injection, 1 mg
J7323	Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose
J7324	Hyaluronan or derivative, Orthovisc, for intra-articular injection, per dose
J7325	Hyaluronan or derivative, Synvisc or Synvisc-One, for intra-articular injection, 1 mg

J7326	Hyaluronan or derivative, Gel-One, for intra-articular injection, per dose
J7327	Hyaluronan or derivative, Monovisc, for intra-articular injection, per dose
J7328	Hyaluronan or derivative, Gel-Syn, for intra-articular injection, 0.1 mg
J7329	Hyaluronan or derivative, trivisc, for intra-articular injection, 1 mg
J7331	Hyaluronan or derivative, SYNOJOYNT, for intra-articular injection, 1 mg
J7332	Hyaluronan or derivative, Triluron, for intra-articular injection, 1 mg

ICD-10 Diagnosis

All diagnoses deny NMN

Document History

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Document History:

- 11/18/2022 – Annual Review: No changes. Coding Reviewed: No changes.
- 11/19/2021 – Annual Review: No changes. Coding Reviewed: No changes.
- 11/20/2020 – Annual Review: No changes. Coding Reviewed: No changes. Effective 4/1/2021 Removed HCPCS J7333.
- 11/15/2019 – Annual Review: No changes. Coding Reviewed: No changes. Coding update. Change to All diagnoses deny NMN. Effective 7/1/2020-Added J7333 for Visco-3. Remove Visco-3 from J7321 6/30/2020
- 8/16/2019 – Coding Review: Added HCPCS code J7331 for Synojoynt (Effective 10/1/19), Added HCPCS code J7332 for Triluron.
- 11/16/2018 – Annual Review: Initial P&T review of ING-CC-0006 Hyaluronan Injections. No changes. HCPCS Coding review: Durolane code change (C9465 to J7318). Add J7329 for TriVisc and updated wording of J7321 to include Visco-3. No ICD-10 changes.

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.