Viscosupplementation

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SCOPE: Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☒ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Viscosupplementation (i.e., hyaluronic acid/hyaluronan injection) is considered **not medically necessary** for all indications, including but not limited to (A.-C.):

A. Osteoarthritis of the knee
B. Osteoarthritis of joints other than the knee (e.g., shoulder, hip, ankle, hand)
C. Temporomandibular joint (TMJ) disorder

Link to Evidence Summary

POLICY CROSS REFERENCES

None

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

BACKGROUND

Osteoarthritis (OA)

According to Hayes, "(o)steoarthritis (OA) is the most common form of articular disease, characterized by degenerative loss of articular cartilage, subchondral bony sclerosis, and cartilage and bone proliferation at the joint margins with subsequent osteophyte formation."[1] Symptoms of OA include

pain in and around the joint that worsens with weight bearing activities and improves with rest. Most commonly, OA affected individuals are older than 40 years old. Although the pathogenesis of OA is unknown, biomechanical stresses, biochemical changes, and genetic factors are possible causes. "OA can affect the temporomandibular joint (TMJ) as well as joints of the appendicular skeleton, including the knee and hip."[1] Treatment of OA includes physical therapy, exercise, nonprescription analgesics, and nonsteroidal anti-inflammatory drugs (NSAIDs). "Joint replacement surgery may be an option for selected patients with severe symptomatic OA who have not responded to medical treatment and who experience progressive limitation in their activities of daily living."[1]

Viscosupplementation (i.e., Hyaluronic Acid/Hyaluronan Injection)

Viscosupplementation involves the injection of a lubricating fluid (e.g., hyaluronic acid/hyaluronan) into a joint.[2] Hyaluronic acid is a key component of healthy joints, and the goal of adding it to an osteoarthritic joint is to facilitate better movement and reduce pain. Viscosupplementation involves the direct injection of hyaluronic acid/hyaluronan into the joint capsule.

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

The U.S. Food and Drug Administration (FDA) indications for use state viscosupplementation is for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy or simple analgesics (e.g., acetaminophen).

The general contraindications and warnings to viscosupplementation include:

- Do not administer to patients with known hypersensitivity (allergy) to hyaluronate preparations.
- Do not administer to patients with known hypersensitivity (allergy) to gram positive bacterial proteins.
- Do not inject in the knees of patients with infections or skin diseases in the area of the infection site or joint.
- Do not administer to patients with known systemic bleeding disorders
- The safety and effectiveness of viscosupplementation in locations other than the knee, and for conditions other than osteoarthritis, has not been established.

Product	HCPCS Code	Dose
Durolane®	J7318	30 mg (3 ml) one time injection
GenVisc® 850	J7320	25 mg once a week (1 week apart) for a total of 5 injections
Hyalgan®	J7321	20 mg once a week (1 week apart) for a total of 5 injections.
Supartz®	J7321	10 mg once a week (1 week apart) for a total of 5 injections.
HYMOVIS®	J7322	24 mg (3 ml) once a week (1 week apart) for a total of 2 injections

Euflexxa®	J7323	20 mg once a week (1 week apart) for a total of 3 injections.
Orthovisc®	J7324	30 mg once a week (1 week apart) for a total of 3 to 4 injections.
Synvisc® (Hylan G-F20)	J7325	16 mg once a week (1 week apart) for a total of 3 injections.
Synvisc-One™ (Hylan G-F20)	J7325	48 mg one time injection.
Synojoynt	J7331	2 mL once a week (1 week apart) for a total of 3 injections.
Gel-One®	J7326	30 mg (3 ml) one time injection
MONOVISC™	J7327	88 mg (4 ml) one time injection
Gel-Syn™	J7328	16.8 mg once a week (1 week apart) for a total of 3 injections
Triluron	J7332	2 mL once a week (1 week apart) for a total of 3 injections.
TriVisc™	J7329	30mg (2.5ml) once a week (1 week apart) for a total of 3 injections
Visco-3	J7333	2.5 mL once a week (1 week apart) for a total of 3 injections.

The U.S. FDA has not approved viscosupplementation for osteoarthritis in other joints (e.g., shoulder, hip, or ankle) or conditions (e.g., temporomandibular joint disorder); therefore, this would be considered an off-label use of hyaluron/hyaluronic acid injections.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of viscosupplementation (i.e., hyaluronic acid injection, hyaluronan injection) as a treatment for osteoarthritis. Below is a summary of the available evidence identified through May 2022.

Osteoarthritis

In 2016, Johansen et al. conducted a systematic review and meta-regression analysis to explore the reasons for the observed inconsistent trial reports on intra-articular injection with hyaluronic acid (IAHA) in the treatment of osteoarthritis, including the knee and hip.[3] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. Study authors were also contacted, if necessary, for additional information or data. The primary outcome of interest was pain. The authors also aimed to identify potential reasons and contextual factors that could explain discordant trial results.

After systematic review, the authors identified 71 studies as eligible for inclusion that also had adequate data available for the meta-analysis (n=11,216). After assessing the risk of bias of included studies using the Cochrane Collaboration bias assessment tool, 64 trials (73%) were determined to have a high risk of bias. The bias assessment also identified six trials (7%) as being free of industry support. A high risk of publication and/or reporting biases was also identified (Eggers test, P<0.001).

The meta-analysis indicated IAHA had a pain reducing effect on the intervention groups compared with the control. However, an analysis of heterogeneity indicated a substantial degree of difference between studies (I^2=73%). The study characteristics found to most significantly impact heterogeneity were overall risk of bias, blinding, and trial size. The authors then stratified by these heterogeneous study characteristics and re-analyzed the effect size. The low risk of bias trials showed no pain reducing effect

after IAHA, whereas the high or unclear risk of bias trials revealed a significant reduction in pain after IAHA. In regards to blinding, a significantly larger treatment effect was observed in unblinded trials compared to blinded trials (-0.70 and -0.23, respectively; P<0.001). Authors indicated, "trial size also had an effect on study results with an effect size of -0.57 in trials with fewer than 100 subjects per treatment group compared to larger trials showing an effect size of -0.21."[3]

Methodological strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, large sample size, contacting study authors for additional information, and assessment of heterogeneity. Limitations were present in the lower methodological quality of available studies and the heterogeneity present between studies. Ultimately, the authors concluded "there is low-quality evidence for the use of hyaluronic acid in pain management among patients with osteoarthritis; the confidence in the effect estimate is limited and the true effect may be substantially different from the estimated effect."[3]

Knee

Systematic Reviews

- In 2021, ECRI conducted an evidence review evaluating the efficacy of viscosupplementation for the treatment of osteoarthritic (OA) knee pain.[4] Investigators searched the literature through for systematic reviews published in 2018 and double-blind RCTs with n>100 not already included in the systematic reviews. In total, 8 systematic reviews and 6 RCTs were included for review.

  Two systematic review (n=2,432) compared intra-articular hyaluronate injections (IAHA) to platelet-rich plasma (PRP) injections for pain reduction. Investigators from the first study (n=1,524 found that PRP injections reduced pain more effectively than HA injections in OA of the knee at 6 months (MD = -14.18; 95% CI: -26.12 to -2.23; p = 0.02; I2=95%) and 12 months (MD=-15.25; 95% CI: -22.17 to -8.32; p <0.01; I2=81%). Visual analog score (VAS) also showed no significant difference at 3 months (MD=-0.98; 95% CI: -2.55 to 0.59; p =0.22; I2=90%) and 6 months (MD = -0.82; 95% CI: -1.80 to 0.16; p =0.1; I2=83%). Investigators stated both treatments' efficacy appeared comparable, but that definitive conclusions could not be drawn due to significant heterogeneity in each calculation, and the variety of evaluation tools across different studies. Investigators from the second study (n=908) found a slightly superior effect among patients receiving PRP injections, versus patients receiving IAHA.

  One SR (n=110 to 39,814) evaluated interventions for knee OA and pain reductions across ten meta-analyses. Compared to non-operative treatments, investigators reported the greatest effect estimates for intra-articular treatments (i.e. PRP and IAHA). While RP provided the greatest point estimate of the treatment effect, variability among studies suggest that future research into optimal treatment parameters was necessary. Investigators concluded that the evidence most strongly supported clinically important and significant treatment effects with IAHA formulations between 1,500 and > 6,000 kDA.

  One SR (n=751) compared IAHA plus corticosteroid (CS) injections to HA alone for pain reduction and function improvement in patients with knee OA. Across eight trials, patients receiving combined CS and IAHA experienced greater pain reduction compared to patients receiving HA alone at 13-month follow-up (SMD 0.25, 95% CI (0.09, 0.41); p = 0.002, I2 = 0%] and [SMD 0.39, 95% CI (0.01, 0.77); p = 0.05, I2= 0%.

One SR (n = 1,004) compared HA with methylprednisolone injection and for pain reduction and function improvement. Across 5 RCTs, no difference was found in pain, physical function and stiffness at 4 week, 12 weeks and 26 weeks between HA and methylprednisolone groups.

One SR (n = 3,485) compared HA with placebo saline injection for pain and adverse events (AEs). Across 20 RCTs, the mean change in pain scores significantly favored IAHA compared to saline injections within 22-27 weeks (SMD = - 0.27, 95% CI - 0.39 to - 0.16, p < 0.00001). However, IAHA was also associated with significantly greater risk of AE's compared to saline (RR = 1.76, CI 1.16-2.67, p = 0.008).

One SR (17 meta-analyses) compared IAHA to placebo injections, measuring outcomes of pain reduction and function improvement. Investigators reported that IAHA provided a moderate symptomatic benefit compared to placebo injections, with an effect size of between 0.30 and 0.40 above that of the IAHA placebo effect. Investigators concluded that future research with long-term follow-up was needed to clarify patient selection criteria.

One SR (n = 3,436) examined repeated IAHA injections for pain reduction maintenance. All 17 articles included for review reported pain reduction from baseline in the IAHA injections throughout the initial treatment cycle, and either sustained or further reduced pain throughout the repeated courses of treatment. Investigators concluded that repeat IAHA injections were safe and provided further pain reduction while also introducing no increased safety risk.
Four RCTs (n = 1,409) not included in the above systematic reviews reported mixed findings across a range of comparisons (e.g. IAHA vs PRP vs. IAHA plus PRP vs. placebo).

ECRI concluded that evidence suggested that IAHA injections may relieve OA knee pain in some patients. Nonetheless, investigators determined that the evidence base regarding the safety and efficacy of the therapy remained inconclusive, and called for additional research to establish treatment parameters, patient selection criteria, and to determine whether IAHA therapy is best used alone or in combination with platelet-rich plasma or corticosteroids.

- In 2021 (archived 2022), Hayes updated a comparative effectiveness review evaluating the safety and efficacy of IAHA – relative to sham IA injections with saline (IAS) or IA injection with corticosteroids (IACS) – for the treatment of osteoarthritis of the knee.[5] Hayes included 4 systematic reviews and 2 RCTs for review. Sample sizes across studies varied from 971 to 4,806 patients; follow-up ranged from 6 weeks to 1 year, with an average of 6 months. Outcomes of interest included time to total knee arthroplasty, pain, function, quality of life (QOL) and complications.

  Two systematic reviews (assessing 123 RCTs) compared the relative safety and efficacy of IAHA and IAS. Both reviews reported clinically important reductions in pain from baseline but not incremental to IAS. A review of 10 RCTs reported superior efficacy of IAHA over IAS in function on average (SMD, –0.23; 95% CI, –0.45 to –0.01), which corresponds to a mean incremental improvement of 8.28 on a 0-to-100 visual analog scale (VAS). A network meta-analysis also concluded that the mean advantage of IAHA was statistically significant, but only clinically relevant depending on the criteria used. Both systematic reviews reported a lack of evidence on

QOL to establish an effect. Two systematic reviews and 2 RCTs compared the relative safety and efficacy of IAHA and IACS.

A network meta-analysis found no significant difference in pain at 3 months after IAHA injections (median effect, 29.44; 95% CrI, 24.17 to 34.93) versus IACS (median effect, 29.00; 95% CrI, 22.63 to 35.15). A pairwise analysis of 8 RCTs assessing 0-to-100 VAS also reported no difference in pain between groups (MD, –0.46;95% CI, –1.31 to 0.39). However, the pairwise analysis also assessed outcomes from 7 RCTs at 6 months follow-up and found significant benefits of IAHA (MD, –0.73; 95% CI, –1.25 to –0.21) and a significant benefit of IAHA over IACS in 4 RCTs at 6 months follow-up (MD, –5.15 (95% CI, –8.77 to –1.54) (p = 0.01). Findings from RCTs published subsequent to these reviews were consistent with these results.

One systematic review and 16 RCTs met inclusion criteria, but as no 2 reviewed studies addressed the same comparison of IAHA products, no evidence-based conclusions could be reached about intra-product efficacy. Hayes concluded that, considered as a whole, there may be no substantive differences in clinical performance among products or types of products (e.g. avian versus bacterial; high versus low molecular weight). No serious or sever complications were associated with IAHA across the studies included for review.

Hayes judged the overall quality of evidence as "moderate" for all comparisons save direct comparisons between IAHA products due to a lack of studies comparing the same 2 treatments. Hayes concluded that IAHA was associated with clinically significant improvements in pain and function; however, no clinically significant benefit in pain control was demonstrated relative to IAS. Investigators ultimately assigned a "C" rating (potential but unproven benefit) for IAHA for the treatment of knee osteoarthritis in patients with chronic symptoms refractory to conservative care.

- In 2017, a workgroup of clinicians published appropriate use criteria evaluating the efficacy of IAHA injections for the treatment of osteoarthritis of the knee.[6] Authors assessed 17 real-world clinical scenarios and determined appropriate use criteria of IAHA for knee OA. Conclusions were made on the basis of an outside systematic review of evidence, current evidence-based practice guidelines and authors' clinical opinion. Authors scored the appropriateness of treatment of each scenario using a 9-point, with 9 as the most appropriate and 1 and the least appropriate. In total, 6 scenarios were scored as appropriate, 10 were scored as uncertain, and 1 scenario was scored as inappropriate. Authors stated that evidence on hyaluronic acid was limited with comparable effects to other active treatments, but appropriate for individuals with mild to moderate disease with symptoms refractory to conservative care. Investigators concluded that additional research was needed to establish treatment parameters and patient selection criteria.

- In 2015, Jevsevar and colleagues conducted a systematic review and meta-analysis to evaluate viscosupplementation for osteoarthritis of the knee.[7] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The primary outcome of interest was the minimal important difference (MID) in the visual analog scale (VAS) and/or Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for pain. The authors also aimed to explore causes of heterogeneous treatment effects in the hyaluronic acid injection (HA) literature.

A total of 19 publications were identified as eligible for inclusion, thus producing a total sample size of 4,485 patients. “Fourteen (74%) of the trials compared HA with placebo (sham treatment), two (11%) compared HA with conventional (usual) care, and three (16%) paired HA with an additional active treatment and compared the results with those in a control group that received that active treatment alone.”[7] Of the selected trials, 63% were industry-funded.

The overall meta-analysis indicated statistically significant heterogeneity due to blinding, HA cross-linking, and follow-up duration. Therefore, the meta-analysis was repeated with stratification by the heterogeneous treatment effects. In regards to blinding, double-blinded sham-controlled trials had much smaller treatment effects compared to trials that were not blinded ($P < 0.05$). For double-blinded trials, the treatment effect was less than half of the MID; therefore, it is unlikely that a substantial number of patients received clinically important benefit. When the meta-analysis was stratified by HA cross-linking, the results indicated the average treatment effect in blinded trials was less than one half the MID whereas the average treatment effect in nonblinded trials was 29% greater than the MID. Lastly, the meta-analysis was stratified by follow-up duration (6 to 13 weeks or >13 weeks). The results indicated the effect size was larger in the trials with follow-up >13 weeks; however, examination of the forest plot indicated this resulted from two trials. These two trials were nonblinded and compared HA with usual care; therefore, they were removed from the analysis. Subsequently, follow-up duration was no longer a significant predictor of HA treatment effect.

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, large sample size, and assessment of heterogeneity. Limitations were identified in the poor quality of included studies, potential for biases, and significant heterogeneity between studies. The authors concluded, “meta-analysis of only the double-blinded, sham-controlled trials with at least sixty patients did not show clinically important differences of HA treatment over placebo. When all literature was added to the analysis, the overall effect was greater but was biased toward stronger treatment effects because of the influence of nonblinded or improperly blinded trials.”[7]

- In 2013, Printz and colleagues conducted a systematic review to “determine the reported rates of both industry sponsorship and financial conflict of interest among the authors of prospective, randomized, placebo-controlled studies on the therapeutic effects of hyaluronic acid injections for knee osteoarthritis.”[8] The authors also, “sought to address whether the qualitative conclusions by the authors about the therapeutic effects of the hyaluronic acid drug were associated with either industry sponsorship or the financial conflicts of interest of the authors.”[8] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data.

  The authors identified 48 publications as eligible for inclusion. The authors used the quantitative conclusions of the selected studies to group the trials into qualitative conclusions. These included favorable (HA was “more effective”, “superior”, or “favorable” compared with placebo), neutral (HA was “effective”, “may be effective”, or “is safe” compared to placebo), or unfavorable (HA was “no more effective” or “not different” compared to placebo). Of the 33 trials that identified a sponsor, 30 were industry sponsored. A total of 31 (65%) had academic authorship while 17 (35%) reported industry authorship, and at least one author affiliated with a pharmaceutical company. Sponsorship was not reported in 15 trials (31%). “Because only three

studies were sponsored by non-industry sources, we were unable to demonstrate any differences among the qualitative conclusion, region, or department of the corresponding author with regard to sponsorship."[8] The results indicated that the qualitative conclusions had a statistically significant association with authorship (p=0.018). Of note, none of the 17 industry-authored studies had an unfavorable conclusion; whereas, 35% of the studies with academic authorship had an unfavorable conclusion.

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers and inclusion of a large number of studies. Limitations are present in the grouping of studies into qualitative data points and lack of conflict of interest disclosure (31%). The authors concluded, "on the basis of our findings in the present review that the qualitative conclusions in studies on hyaluronic acid injections for knee osteoarthritis were commonly associated with industry authorship, clinicians should be aware of the potential financial conflicts of interest of the authors reporting on this topic and carefully evaluate the recommendations from these studies based on the objectivity of the study design."[8]

- In 2012, Rutjes et al. conducted a systematic review and meta-analysis to determine whether viscosupplementation is clinically effective and safe to treat symptomatic knee osteoarthritis.[9] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. Study authors were also contacted, if necessary, for additional information or data. The primary outcome of interest was pain, while physical function and serious adverse events were the secondary outcomes of interest.

  After systematic review, the authors had identified 177 publications describing 89 trials in 12,667 patients as eligible for inclusion. "Thirteen trials reported adequate concealment of allocation (15%), 68 trials used a sham intervention in the control group (76%), 16 were judged to have adequately blinded patients (18%), and 48 had blinded outcome assessment (54%). Seventeen trials had analyzed all patients according to the intention-to-treat principle (19%), and 23 trials had sample sizes of 100 patients or more per trial group (26%)."[9]

  The overall meta-analysis for pain indicated that viscosupplementation had a moderate effect size, which met the pre-specified clinically important difference; however, there was a statistically significant degree of heterogeneity between trials (P<0.001). Due to the heterogeneity, the authors conducted stratified analyses for larger trials (>100 participants per trial group), adequately blinded trials, and larger trials with adequate blinding. After stratification by these three study characteristics, the effect size did not reach the minimal clinical important difference for any subgroup. The meta-analysis of physical function indicated that viscosupplementation had a moderate effect; however, the trials were also statistically significantly heterogeneous. After stratifying by larger trials and adequately blinded trials, the minimal clinically important difference was again not reached. The results of the meta-analysis evaluating safety suggested that viscosupplementation was associated with an increased risk of adverse events.

  Methodological strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, large sample size, and assessment of heterogeneity. Significant limitations were present due to the poor

quality of many included studies, inadequate data reporting by many studies, and significant inter-study heterogeneity. The authors also stated "Many reports did not provide adequate data on adverse events, which is concerning in light of the observed safety signals. The low quality of reporting of safety data means that we could not understand the probable causes of serious adverse events."[9] Ultimately, the authors concluded that, "viscosupplementation is associated with a small and clinically irrelevant benefit and an increased risk for serious adverse events."[9]

Multiple Treatment Effects

Systematic Reviews

In 2016, Bannuru et al. conducted a systematic review to evaluate the safety of repeated injections of Supartz® for knee osteoarthritis.[10] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The primary outcome of interest was overall incidence of adverse events. The authors also evaluated adverse events reported separately by type and severity.

After systematic review, the authors had identified 6 nonrandomized studies as eligible for inclusion (1 postmarket registry [n=7404], 4 prospective studies [n=127], 1 retrospective study [n=220]). The results of the postmarket registry reported 58 adverse events, most occurring after the first course of treatment. "Local reactions included pain (29), swelling (16) and redness (3). Other reactions were rash (3), itching (1), increased serum glutamic oxaloacetic transaminase (2), increased serum glutamic-pyruvic transaminase (3), and increased alkaline phosphatase (1)."[10] The 4 prospective studies included in the systematic review reported no adverse events or abnormal lab results related to Supartz®. The retrospective study reported a total of 26 adverse events (20 mild and 6 moderate) in 303 knees. All but one adverse event were determined to be related to the injection. The most serious reactions included arthralgia (2), swelling (1), stiffness (1), and fainting (1). The most common mild adverse events were skin ecchymosis (11), pain (5), swelling (2), blistering (1), and nausea (1). After pooling the data, the overall adverse event rate following repeat courses of Supartz® was determined to be 0.008; however, there was significant heterogeneity between studies (I^2=73%).

Strengths of this study include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers and the assessment of heterogeneity. However, the reliability of conclusions drawn from this study is hindered due to several limitations. These include, but are not limited to, the following:

- Poor methodological quality of included studies (lack of randomization, retrospective designs, small sample sizes, and short follow-up periods)
- Probable publication bias due to the small number of selected studies
- Only 1 of 10 commercially available hyaluronic acid products were evaluated
- 5 of the 6 selected studies took place in Japan
- Meta-analysis was conducted inappropriately due to significant between study heterogeneity, and no statistical methods were used to account for this heterogeneity
- Conflicts of interest and probable funding bias due to the study authors being supported by the Supartz® manufacturer (Bioventus®, Inc.)

Due to the poor methodological quality, high risk of bias, and lack of generalizability, this systematic review does not permit meaningful conclusions regarding the efficacy and safety of repeat hyaluronic acid injections to treat knee osteoarthritis.

In 2017, Concoff and colleagues conducted a systematic review and meta-analysis evaluating the safety and efficacy of multiple versus singly IAHA injections for the treatment of knee OA.[11] Independent investigators systematically searched the literature though February 2016, identified eligible studies, assessed study quality, extracted data and pooled results. The primary outcome of interest was mean knee pain score at 3 months or 6 months. In total, 30 articles (n= 5,848) were included for review. Four studies (n =1,996) used single injections of IAHA, 16 studies (n=2,865) used 2-4 injections and 11 studies (n=1,847) evaluated 5 or more injections. Compared to patients receiving IA-Saline (IAS), patients receiving 2-4 injections of IAHA experienced superior outcomes at 3- and 6-month follow-up (SMS = -0.76; -0.98 to -0.53, 95% CI, p < 0.00001, and SMD = -0.36; -0.63 to-0.09 95% CI, p =0.008 respectively). While single injection studies reported no significant effect at 3- and 6-month intervals, patients receiving 5 or more injections experienced significant improvements in pain, although only at 6-month follow-up. Five or more IAHA injections were also associated with a higher risk of treatment-related AEs compared to IA-Saline (RR =1.67; 1.09 to 2.56 95% CI, p =0.02). This result was not seen within the 1 and 2-4 injection subgroups.

Study limitations included industry-funding of a majority of the reviewed RCTs, as well as a lack of a direct comparison between the exact numbers of injections received by individual patients, due to a lack of robust data in the reviewed studies. Inconsistent reporting of pain scores, variable follow-up times, and heterogeneity within some subgroups may have also biased results. Investigators concluded that injection regimens of 2-4 and at least 5 provided pain relief superior to patients receiving IAS, whereas patients receiving single injection did not. Intra-articular injections of HA used in a 2-4 injection treatment regimen provided the greatest benefit when compared to IA-Saline with respect to pain improvement in patients with knee OA, and was generally deemed safe with few to no treatment-related AEs reported across studies. Investigators called for additional research to further compare treatment regimens in head-to-head RCTs, evaluating alternative outcomes such as function and stiffness.

Randomized Controlled Trials (RCTs)

- In 2011, Altman et al. conducted a multicenter, open-label, randomized trial to evaluate the safety of repeated series of intra-articular Euflexxa® (IA-BioHA).[12] IA-BioHA is a non-cross linked high molecular weight hyaluronan. A total of 433 subjects were recruited from the already randomized cohort of the FLEXX RCT. A total of 214 subjects were treated with intra-articular hyaluronic acid (IA-HA) while 219 were treated with IA-BioHA. The primary outcome of interest was safety, which included treatment emergent adverse events (TEAE), laboratory parameters, vital signs, and physical examination of the knee. The authors also evaluated efficacy as a secondary outcome of interest. Participant follow-up lasted for 26 weeks.

  A total of 11 subjects discontinued the study due to AEs (5), withdrew consent (2), and lost to follow-up (4). Overall, 43.3% of subjects reported at least one TEAE during the 26 weeks of follow-up. “The AEs that occurred most often in the Extension Study were arthralgia (9.9%), injury (4.4%), nasopharyngitis (3.5%), upper respiratory infections (3%), and joint swelling in the soft tissue at the injection site (2.3%).”[12] Among the subjects with at least one AE, 21 (4.8%) were determined to be related to the IA-BioHA. The most common IA-BioHA related AEs were arthralgia (2.8%), joint swelling (1.2%), peripheral edema (0.7%), and injection site pain (0.5%).

In regards to efficacy, patients who continued with IA-BioHA or IA-HA from the FLEXX study maintained pain reduction from baseline.

Strengths of this study include the multicenter, randomized controlled design and large sample size. The authors concluded "repeat injections of IA-BioHA were effective, safe, well tolerated, and not associated with an increase in AEs." However, significant methodological limitations affect the validity of these conclusions. The short follow-up period, lack of blinding, and lack of a placebo comparator group create substantial sources of bias. Funding bias is also probable due to the study being supported by the Euflexxa® manufacturer (Ferring Pharmaceuticals, Inc.) and several author conflicts of interest.

- In 2010, Jorgensen et al. conducted a multicenter, randomized, placebo-controlled, double-blind study to evaluate the long-term efficacy and safety of five intra-articular injections with the hyaluronan product Hyalgan® compared with placebo.[13] Power calculations indicated 151 patients in each treatment group would be needed to detect a clinically relevant difference; thus, 337 patients with osteoarthritis of the knee joint were recruited to participate. Patients were randomized 1:1 to receive either Hyalgan® (n=167) or saline placebo (n=170) injections weekly for 5 weeks. The syringes were pre-packaged to mask treatment identify to both the patient and physician. All patients were followed for 3 months after the first injection, and those still benefiting from treatment at 3 months were followed until "time to recurrence" or a maximum of 1 year. The primary outcome measure was time to recurrence (the time from the start of improvement until recurrence of the Lequesne algofunctional index score [LFI]). Time to recurrence was evaluated at 3, 6, 9, and 12 months. Secondary outcome measures included visual analog score (VAS) pain during a 50m walk, paracetamol consumption, patients' global assessment, responder rates, and adverse events (AEs).

  Treatment compliance was observed in 95% of the hyaluronan group and 99% in the placebo group. The mean time to recurrence was 172 days for the hyaluronan group and 204 days for the placebo group (no significant treatment effect, p=0.26). At 3 months follow-up, 31.1% of the hyaluronan group was non-responders while 27.6% of the placebo group; therefore, these patients were excluded from additional follow-up (in accordance with the pre-defined study parameters). Additionally, no significant change from baseline was identified in LFI or VAS pain during the 50 m walk. These two parameters also showed no significant treatment effect. No significant difference between treatment groups was identified for paracetamol consumption, patients' global assessment, responder rates, or adverse events (AEs).

  This study has several methodological strengths, including:

  - Robust study design: randomized, multi-center, double-blinded, and placebo-controlled
  - The use of intention-to-treat analysis
  - Large sample size
  - Use of an internationally validated index for scoring pain and function
  - Adequately powered to determine a clinically relevant difference

  Limitations include the shorter-follow up period for some participants, losses to follow-up (6%), subjective primary outcome measure, and evaluation of only one commercially available

hyaluronan product. Ultimately, the authors concluded that in patients with moderate to severe osteoarthritis of the knee "five intra-articular injections of hyaluronan did not improve pain, function, paracetamol consumption or other efficacy parameters 3, 6, 9 and 12 months after the treatment."[13]

Nonrandomized Studies

Four nonrandomized studies were identified that evaluated the efficacy and safety of multiple hyaluronic acid injections.[14-17] Although these studies suggest multiple injections of hyaluronic acid may improve pain and physical function, the validity of these conclusions is significantly limited due to the poor study quality. All studies are nonrandomized (2 prospective, 2 retrospective) observational studies that do not use a placebo control group. Two studies have very small sample sizes (<100 patients) and short follow-up periods. Due to the study design being a retrospective database review, two studies significantly lack baseline and endpoint data. Due to the aforementioned limitations, meaningful conclusions cannot be drawn; therefore, these studies are insufficient to support the efficacy, safety, or medical necessity of multiple hyaluronic acid injections.

Delay to Total Knee Replacement

Systematic Reviews

In 2015, Newberry and colleagues as part of the Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review ,"of the evidence that intraarticular injections of hyaluronic acid (HA) in individuals with degenerative joint disease (osteoarthritis [HA]) of the knee improve function and quality of life (QoL) and that they delay or prevent the need for total knee replacement (TKR)."[18] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data.

After systematic review, the authors identified 16 studies (3 randomized controlled trials [RCTs] and 13 nonrandomized observational studies) as eligible for inclusion. The author's systematic review also identified several case series that reported on the average or longest time to TKR in HA treated patients; however, these studies were not included because they did not meet the study design inclusion criteria (randomized controlled trial or observational study). Only one of the RCTs reported delay or avoidance of TKR as a pre-defined primary outcome of interest, whereas the other RCTs reported it as a treatment failure. All but one study were determined to have a high risk of bias. Results of the two high-risk bias RCTs demonstrated a non-significant trend, indicating that fewer people in the treatment group had knee replacement compared to the placebo group. The third RCT showed no statistically significant difference in time to TKR in the HA group compared to the placebo group (p=0.249). The 13 nonrandomized studies (6 retrospective case series and 7 cohort studies) reported mixed results, with treatment failure (i.e., total knee replacement) rates ranging from 1% to 32.9%. An assessment of bias in the nonrandomized studies indicated all had a moderate to high risk of bias. The authors stated, "few studies attempted to control for baseline differences in comorbidities, few reported financial conflicts of interest, and patients were aware of their treatment in every instance."[18]

Methodological strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, and assessment of heterogeneity prior to conducting meta-analyses. Limitations are present in the poor methodological quality of included studies (lack of randomization, lack of blinding, lack of control group, small sample sizes, and short

follow-up periods), inadequate data reporting of included studies, and identification of only one RCT with TKR as the primary outcome. Ultimately, the authors stated, "no conclusions can be drawn from the available literature on delay or avoidance of TKR through the use of HA. Studies that can compare large numbers of treated and untreated individuals, preferably with a randomized design, are needed to answer this question."[18]

Randomized Controlled Trials (RCT)

The evidence review identified one RCT that assessed intra-articular hyaluronic acid injections and delay to total knee replacement as the primary outcome of interest.[19] This RCT was included in the systematic review described above; therefore, it will not be discussed here.

Nonrandomized Studies

The evidence review identified 5 nonrandomized studies, not included in the Newberry et al. systematic review, which evaluated intra-articular hyaluronic acid (HA) injections and delay to total knee replacement (TKR) as the primary outcome of interest.[20-24] All studies concluded that HA injections in patients with knee osteoarthritis was associated with an increase in time to TKR. However, the reliability of this conclusion is significantly limited due to the poor methodological quality of these studies. All studies were retrospective database reviews, which significantly limits the availability of baseline and endpoint data. Furthermore, no studies used randomization or a comparison/control group. Prospective studies of good methodological quality (e.g., large sample size, randomized, placebo-controlled) are required in order to support the hypothesis that HA injections delay or prevent TKR.

Shoulder

In 2014, Colen et al. conducted a systematic review and meta-analysis of the literature to evaluate intra-articular (IA) infiltration therapy for patients with glenohumeral (shoulder) osteoarthritis (GH-OA).[25] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The primary outcomes of interest were pain, physical function, and patient global assessment. When reported, adverse events were included as a secondary outcome.

After systematic review, the authors had identified 8 studies (2 randomized controlled trials, 5 prospective case series, and 1 retrospective observational study) as eligible for inclusion (n=895). Of the 895 patients included in the systematic review, 579 received hyaluronic acid (HA), 33 received corticosteroids (CS), and 283 received phosphate-buffered saline (PBS). After pooling the data, "HA showed effect sizes of 2.07, 2.02 and 2.11 at 6-, 12- and 26-weeks follow-up, respectively."[25] At 6, 12, and 26 weeks follow-up, placebo also showed consistent effect sizes (1.60, 1.82, and 1.68). Although HA demonstrated consistent efficacy through 26 weeks, the difference in efficacy between HA and placebo never reached the minimal clinically important difference at any follow-up point. The effect size of CS decreased rapidly at the follow-up points (1.08, 0.43, and 0.19). No serious adverse events were reported. Mild adverse events included local pain and local reaction at the injection site.

Methodological strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers. Significant limitations are present in the poor methodological quality of selected studies, small number of selected studies (potential publication bias), and not assessing heterogeneity before conducting meta-analyses. The authors concluded "the difference in efficacy between HA and placebo never reaches the minimal clinically important difference at any of the follow-up points. In future research, we recommend focusing on

sufficiently powered randomized trials to compare the efficacies of HA, CS, placebo and other IA treatment options in patients with GH-OA."[25]

Hip

- In 2020, Acuña and colleagues published a systematic review of patient-reported outcomes from viscosupplementation for hip osteoarthritis.[26] Thirty-nine studies were included in the review, totalling 5864 patients receiving hyaluronic acid (HA) injections. The Lequesne Index measuring pain and function in osteoarthritis was evaluated in 16 studies, 15 of which reported decreases in score (i.e. improvement) after HA injections, 12 with significant reductions. Visual analog scale was evaluated in 29 studies, 19 of which found significant reductions in VAS scores after treatment with HA. The Western Ontario and Mcmaster Universities Osteoarthritis Index (WOMAC) was evaluated in 18 studies, a majority of which found improvement in pain and function after viscosupplementation. Six studies analyzed Harris Hip Score, 4 of which found significant improvement over time after HA injections. The studies included in the systematic review largely lacked comparator groups, and there was mixed evidence when comparing viscosupplementation to PRP, corticosteroids, or placebo. There was also a lack of evidence showing that viscosupplementation delays total hip arthroplasty. Limitations of the review include a lack of randomized trials, potential bias from a industry-funded studies, heterogeneity in treatment protocols and methodology, small sample sizes, and inadequate follow up among some included studies. The authors concluded that "there was not enough evidence in the current literature regarding whether HA is superior to placebo or other types of intra-articular injections. Future studies should continue to compare HA to other treatment modalities in randomized controlled trials with larger sample sizes."[26]

- In 2018, Leite and colleagues conducted a systematic review and meta-analysis evaluating the safety and efficacy of IAHA injections for the treatment of pain and disability caused by hip osteoarthritis.[27] Independent investigators systematically searched the literature though February 2017, identified eligible studies, assessed study quality, extracted data and conducted a random-effects meta-analysis.

  In total, 8 RCTs were included for review (n=807): 4 of which compared IAHA to placebo; 3 to platelet-rich plasma (PRP); 3 to methylprednisolone; and 1 to mepivacaine. Investigators stated that very low quality evidence indicated that IAHA is not superior to placebo for pain at 3 months. Investigators found very low quality evidence indicating that IAHA is not superior to placebo for pain at 3-months follow-up (SMD=-.06; 95% CI, -.38 to .25; *p* =.69), and high quality evidence that IAHA patients do not experience more adverse events (RR 1.21; 95% CI, .79-1.86; P=.38). Compared to PRP, very low quality evidence suggested that that IAHA is not superior for the treatment of pain at 6 and 12 months (MD in VAS [in cm]: -.05 [95% CI, -.81 to .71], 1.0 [95% CI, -1.5 to 3.50], and .81 [95% CI, -1.11 to 2.73], respectively). Compared to patients receiving methylprednisolone, high quality evidence indicated that IAHA patients experienced no significant difference at 1-month follow-up in pain (SMD=.02; 95% CI, -.18 to .22; *p* = 0.85) or adverse events (RR=1.21; 95% CI, .79-1.87; *p* = 0.38). Study limitations included reviewed studies' small sample sizes and heterogeneous patient selection criteria. Investigators ultimately recommend against the use of viscosupplementation for the treatment of hip osteoarthritis, given the lack of demonstrated efficacy at either 3- or 6 month follow-up.

- In 2015, Lieberman and colleagues conducted a systematic review and meta-analysis to evaluate the efficacy of hyaluronic acid (HA) injections to treat hip pain due to osteoarthritis.[28] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The authors aimed to evaluate (1) Does the treatment of OA of the hip via viscosupplementation with hyaluronic acid decrease pain in the hip joint compared to placebo or other agents? (2) What is the duration of the pain relief associated with HA injections to the hip? (3) Is one of the HA formulations clearly superior with respect to pain relief?

  After systematic review, the authors identified 23 studies that were eligible for inclusion (6 randomized controlled trials [RCTs], 15 prospective observational studies, and 2 retrospective observational studies). The meta-analysis indicated that, on average, subjects reported a statistically significant decrease in pain (-1.97, $p<0.0001$). A separate analysis of the 6 RCTs indicated a slight pain improvement in favor of HA when compared to the controls (-0.27, $p=0.001$). The authors noted it was difficult to determine the clinical relevance of this change because the follow-up duration in most studies was less than 6 months.

  Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers and the large number of included studies. Methodological limitations are present in the poor quality of selected studies and not assessing heterogeneity prior to pooling the data. Ultimately, the authors concluded "multicenter randomized trials are needed to determine the true efficacy of HA injections in decreasing pain associated with hip osteoarthritis."[28]

Ankle

In 2015, Witteveen et al. conducted a Cochrane systematic review to assess the benefits and harms of hyaluronic acid (HA) and other conservative treatment options for osteoarthritis (OA) of the ankle.[29] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. Study authors were also contacted, if necessary, for additional information or data. The primary outcomes of interest were pain and physical function (measured with the Ankle Osteoarthritis Scale [AOS]). Secondary outcomes of interest included quality of life and adverse events.

The authors identified six randomized controlled trials evaluating HA for ankle OA that met inclusion criteria (n=240). No RCTs were identified that evaluated other conservative treatment options for ankle OA. Three of the included studies compared HA to placebo, one compared HA to exercise therapy, one compared HA combined with exercise therapy to an intra-articular injection of botulinum toxin, and one compared four different dosages of HA. The pooled analysis indicated that the AOS total score was reduced by 12% at six months. However, the evidence was rated as low quality due to study design limitations. Also, no minimal important clinical difference was identified. Missing data did not permit meta-analysis for the quality of life outcome. No serious adverse events were reported. The results were inconclusive for the RCT comparing HA to exercise therapy and the RCT comparing HA injection combined with exercise therapy to an intra-articular injection of botulinum toxin. The RCT comparing for different dosages of HA found the best median decrease in pain when participants were given 1mL injections 3 times; however, 27% of participants had adverse events.

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers following the Cochrane methodology. However, methodological limitations are present in the poor quality of included studies, the small number of included studies, and the small sample size. The authors concluded "it is unclear if there is a benefit or

harm for HA as treatment for ankle OA compared to placebo at six months based on a low quality of evidence. Inconclusive results were found comparing HA to other treatments."[29]

Hand

In 2016, Kroon and colleagues conducted a systematic review and meta-analysis of the literature to evaluate the efficacy and safety of intra-articular (IA) therapies for the treatment of carpometacarpal (CMC) and interphalangeal (IP) osteoarthritis (OA).[30] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. The primary outcome of interest was pain on a visual analog scale (VAS) or a numerical rating scale (NRS). Secondary outcomes included self-reported physical function, patient global assessment, joint activity, health-related quality of life, hand strength, and adverse events (AEs).

The authors identified 13 studies including 864 participants as eligible for inclusion. Of these 13 studies, 3 trials compared hyaluronic acid (HA) with placebo, 6 trials compared corticosteroids (CS) with HA, and 4 trials compared CS with placebo. After assessing heterogeneity, it was determined that most studies were too heterogeneous to compare, did not provide data eligible for meta-analysis, and/or the risk of bias was determined to be too high. The 3 trials evaluating HA with placebo showed a decrease in pain compared with baseline in both groups; however, no statistically significant between group difference were identified through 26 weeks for any efficacy outcome. The trials evaluating CS compared to HA all showed an improvement in pain from baseline in both treatment groups; however, 4 trials showed no statistically significant between group differences, 1 trials found CS to be superior to HA, and 1 trial had inconclusive results. Only local AEs were reported in all trials, and no treatment was reported to be more harmful than another.

Methodological strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, and assessment of heterogeneity prior to conducting meta-analyses. Limitations are present in the poor methodological quality of included studies, inadequate data reporting of included studies, small number of included studies (probable publication bias), and the inability to conducted meta-analyses due to significant heterogeneity. Ultimately, the authors concluded "despite a beneficial short-term safety profile, IA CS or HA do not appear more effective than placebo in CMC OA."[30]

Temporomandibular Joint (TMJ)

- In 2018, Ferreira and colleagues conducted a systematic review evaluating the safety and efficacy of IAHA injections for the treatment of temporomandibular dysfunctions.[31] Independent investigators systematically searched the literature though April 2017, identified eligible studies, assessed study quality and extracted data. In total, 21 articles were included for review (n=30 to 121) reported mixed findings. However, definitive conclusions from these results could not be establish due to studies' heterogeneity of intervention type, comparator groups and the varying molecular weight of IAHA compounds. Other limitations of reviewed studies included small sample sizes, and high risk of bias among 9 included studies due to poor methodological design. Investigators called for the standardization of therapeutic protocols and uniform follow-up periods.

- In 2017, Iturriaga et al. conducted a systematic review to assess the effects of hyaluronic acid (HA) on the regulation of inflammatory mediators in osteoarthritis (OA) of the temporomandibular joint (TMJ).[32] Independent reviewers systematically identified eligible

studies, assessed quality, and extracted data. The primary outcome of interest was the regulation of inflammatory mediators (specifically urokinase-type plasminogen activator system [uPA] and nitric oxide [NO]) after the application of HA.

After systematic review, the authors identified 2 publications as eligible for inclusion (n=87). The first publication evaluated uPA, and the second publication evaluated NO. In regards to uPA, a decrease in uPA activity was observed after treatment with HA compared to before treatment. When comparing the HA group to the placebo group, there was also a significant between group difference in uPA activity. A statistically significant correlation as also identified between the decrease in pain intensity reported by patients and uPA activity. In evaluating NO, a decrease in NO levels was identified in patients treated with HA; however, no statistically significant differences were identified when compared to the placebo group.

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers. However, significant methodological limitations are present in the small number of selected studies (probable publication bias), small sample size, and the poor quality of these selected studies. The authors concluded "the limited evidence available suggests that the application of HA regulates various inflammatory mediators in osteoarthritic processes in the TMJ. Nevertheless, further evidence in this regard is required, through the study of specific pathologies of the TMJ, complementing the assessment of clinical parameters with molecular studies, and generating good quality clinical studies with larger sample sizes."[32]

CLINICAL PRACTICE GUIDELINES

Osteoarthritis

National Institute for Health and Care Excellence (NICE)

The 2022 NICE evidence-based clinical practice guideline on osteoarthritis recommended against the use of viscosupplementation stating, "do not offer intra-articular hyaluronan injections for the management of osteoarthritis."[33]

Department of Veterans Affairs/Department of Defense (VA/DoD)

The 2020 VA/DoD evidence-based clinical practice guideline on intra-articular injections gave the following recommendations for hyaluronic acid injections:[34]

13. "We suggest offering an intra-articular viscosupplementation injection(s) for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions. (Weak for | Reviewed, New-replaced)"
14. We suggest against the use of intra-articular viscosupplementation injection(s) of the hip. (Weak for | Reviewed, New-replaced)"

"Given the potential benefits, acceptable small number of adverse events, and patient preferences and resource use, the Work Group decided upon a "Weak for" recommendation for Recommendation 13. Conversely, given the increased burden of hip injections requiring image guidance and increased

specialization to administer, the risk of local injury to neurovascular structures, and the lack of demonstrated benefit, the Work Group decided upon a "Weak against" recommendation for Recommendation 14.

The research gaps regarding VSIs include a relative lack of long-term adverse event studies beyond one year. Additionally, further studies are needed to determine optimized dosing schedules. Lastly, there is insufficient evidence on efficacy and safety in VSI use for hip OA, even in the short-term."

Knee

Health Evidence Review Commission (HERC) - Oregon

In 2019, HERC issued an evidence-based coverage guidance addressing interventions for osteoarthritis of the knee, and recommended that glucosamine and/or chondroitin (i.e. viscosupplementation) not be covered .[35]

Canadian Agency for Drugs and Technologies in Health

In 2017, the Canadian Agency for Drugs and Technologies in Health conducted a non-systematic literature review evaluating the efficacy of viscosupplementation for the treatment of knee arthritis.[36] Investigators found evidence for the use of IAHA in adults with knee OA to be conflicting, with no significant difference in efficacy between various IAHA agents and placebos.

Colorado Division of Worker's Compensation

The 2016 Colorado Division of Worker's Compensation evidence based clinical practice guideline on lower extremity injuries stated, "Due to lack of efficacy, viscosupplementation for knee is not recommended and requires prior authorization."[37]

Osteoarthritis Research Society International (OARSI)

The 2019 OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis stated, "Intra-articular Hyaluronic Acid (IAHA) is conditionally recommended for longer term treatment effect, as it was associated with symptom improvement beyond 12 weeks and demonstrated a favorable safety profile."[38] (Level 1B/Level 2, conditional) The guidelines did not cite evidence-based data to support the conditional recommendation. The guidelines did not cite evidence-based data to support the conditional recommendation.

American Academy of Orthopedic Surgeons (AAOS)

The 2021 AAOS evidence-based clinical practice guideline on the treatment of osteoarthritis of the knee stated, "hyaluronic acid intra-articular injection(s) is not recommended for routine use in the treatment of symptomatic osteoarthritis of the knee (strength of recommendation: moderate)."[39]

Shoulder

Colorado Division of Worker's Compensation

The 2015 Colorado Division of Worker's Compensation evidence-based clinical practice guideline for shoulder injury treatment gave the following recommendations:[40]

- "There is insufficient evidence of the effectiveness of hyaluronate in rotator cuff tendinopathy, therefore it is not recommended for this condition.
- There is some evidence that hyaluronic acid (HA) added to physical therapy (PT) does not improve symptomatic and functional outcomes of adhesive capsulitis over the improvements seen with PT alone. Therefore, it is not recommended.
- There is good evidence that subacromial injection of hyaluronic acid is not more effective than steroid or placebo for pain relief and functional improvement of subacromial impingement syndrome. Therefore, it is not recommended."

The guideline also stated the U.S. FDA has not approved viscosupplementation for use in the shoulder.

American Academy of Orthopedic Surgeons (AAOS)

The AAOS evidence-based clinical practice guidelines on the treatment of glenohumeral joint osteoarthritis were updated in 2020.[41] The authors gave a strong recommendation regarding hyaluronic acid, stating, "Strong evidence supports that there is no benefit to the use of hyaluronic acid in the treatment of glenohumeral joint osteoarthritis."

Hip

American Academy of Orthopedic Surgeons (AAOS)

The 2017 AAOS evidence-based clinical practice guideline on the management of osteoarthritis of the hip stated, "strong evidence does not support the use of intraarticular hyaluronic acid because it does not perform better than placebo for function, stiffness, and pain in patients with symptomatic osteoarthritis of the hip. Strength of Recommendation: Strong Evidence"[42]

Colorado Division of Worker's Compensation

The 2016 Colorado Division of Worker's Compensation evidence based clinical practice guideline on lower extremity injuries stated "viscosupplementation is not recommended for hip arthritis given the probable superiority of corticosteroid injections."[37]

Ankle

Colorado Division of Worker's Compensation

The 2016 Colorado Division of Worker's Compensation evidence based clinical practice guideline on lower extremity injuries stated, "there is inadequate evidence that hyaluronic acid is more effective than saline for treatment of ankle osteoarthritis. Hyaluronic acid injections are, therefore, not recommended for ankle osteoarthritis due to the small effect size documented in knee conditions and the lack of evidence supporting its use in the ankle."[37]

EVIDENCE SUMMARY

Osteoarthritis of the Knee

Current evidence does not demonstrate the use of hyaluronic acids are more effective than placebo or other conservative therapies at reducing pain and increasing physical function in patients with osteoarthritis of the knee. Despite the large quantity of literature, there is a lack of definitive treatment benefit and no standardized treatment protocol due to discordant findings. Also, the validity of several studies is significantly affected by poor methodological quality and considerable risks of bias, including industry sponsorship.

In addition, current evidence does not demonstrate treatment benefit of multiple treatment courses of hyaluronic acids. The literature on multiple injections is conflicting, and is significantly hindered by poor methodological quality and biases. There is also a lack of consensus regarding the ideal treatment regimen and patient population for multiple injections, making it difficult to evaluate the effectiveness.

Finally, current evidence does not support the purported benefit of viscosupplementation in the delay or prevention of total knee replacement. The available evidence evaluating this hypothesis is limited and of poor methodological quality. A 2015 Agency for Healthcare Research and Quality systematic review concluded insufficient evidence supporting the delay or avoidance of total knee replacement through the use of hyaluronic acid. The AHRQ systematic review identified three randomized controlled trials; however, only one evaluated time to total knee replacement as the primary outcome of interest. This study (quality assessed as low risk of bias) found no statistically significant difference at one year between hyaluronic acid and placebo in delaying time to total knee replacement. Prospective studies of good methodological quality (e.g., large sample size, randomized, placebo-controlled) are required in order to support the hypothesis that hyaluronic acid injections delay or prevent total knee replacement.

No evidence-based clinical practice guidelines make definitive recommendations for the use of viscosupplementation for the treatment of knee osteoarthritis. The National Institute for Health and Care Excellence, Colorado Division of Worker's Compensation, Osteoarthritis Research Society International, and the American Academy of Orthopedic Surgeons recommend against the use of viscosupplementation. Therefore, viscosupplementation for knee osteoarthritis is considered not medically necessary.

Other Joints

The evidence is insufficient to support viscosupplementation as a treatment of osteoarthritis in other joints (e.g., shoulder, hip, ankle, hand) or conditions (e.g., temporomandibular joint disorder). Further studies of good quality are required in order to establish the safety, effectiveness, and medical necessity of hyaluronic acid injections for these conditions. Furthermore, the U.S. Food and Drug Administration have only approved hyaluronic acid as a treatment of osteoarthritis of the knee; therefore, these would be considered an off-label use of the drug.

Evidence-based clinical practice guidelines recommend against the use of viscosupplementation as a treatment of osteoarthritis in other joints.

BILLING GUIDELINES AND CODING

If CPT codes 20600, 20604, 20605, 20606, 20610, or 20611 are billed in conjunction with viscosupplementation they will also be denied as not medically necessary.

CODES*		
CPT	20610	Arthrocentesis, aspiration and/or injection, major joint or bursa (eg, shoulder, hip, knee, subacromial bursa); without ultrasound guidance
	20611	Arthrocentesis, aspiration and/or injection, major joint or bursa (eg, shoulder, hip, knee, subacromial bursa); with ultrasound guidance, with permanent recording and reporting
HCPCS	J7318	Hyaluronan or derivative, durolane, for intra-articular injection, 1 mg
	J7320	Hyaluronan or derivitive, 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, gelsyn-3, for intra-articular injection, 0.1mg
	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
	J7333	Hyaluronan or derivative, visco-3, for intra-articular injection, per dose
	J3490	Unclassified drugs

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
8/2023	Annual update. No changes to criteria or codes.