Medical Policy

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Title: Intra-Articular Hyaluronan Injections for Osteoarthritis

Related Policies:	▪ *Temporomandibular Joint (TMJ) Disorder*

Professional / Institutional
Original Effective Date: January 2001 / July 1, 2007
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Populations	Interventions	Comparators	Outcomes
Individuals: • With osteoarthritis of the knee	Interventions of interest are: • Intra-articular hyaluronan injections	Comparators of interest are: • Physical therapy • Medication • Surgery • Intra-articular corticosteroids	Relevant outcomes include: • Symptoms • Functional outcomes • Treatment-related morbidity
Individuals: • With osteoarthritis of joints other than the knee	Interventions of interest are: • Intra-articular hyaluronan injections	Comparators of interest are: • Physical therapy • Medication • Surgery • Intra-articular corticosteroids	Relevant outcomes include: • Symptoms • Functional outcomes • Treatment-related morbidity

DESCRIPTION

Intra-articular injection of hyaluronan into osteoarthritic joints is proposed to reduce pain and improve function. It is thought to replace endogenous hyaluronan and restore the viscoelastic properties of the synovial fluid. Most studies to date have assessed hyaluronan injections for knee osteoarthritis, the U.S. Food and Drug Administration approved indication. Other joints (e.g., hip, shoulder) are being investigated for intra-articular hyaluronan treatment of osteoarthritis.

OBJECTIVE

The objective of this evidence review is to determine whether intra-articular injection of hyaluronan improves the net health outcome in individuals with osteoarthritis of the knee and other joints (e.g., hip, shoulder).

BACKGROUND

Knee Osteoarthritis

Knee osteoarthritis is common, costly, and a cause of substantial disability. Among U.S. adults, the most common causes of disability are arthritis and rheumatic disorders.

Treatment

Currently, no curative therapy is available for osteoarthritis, and thus the overall goals of management are to reduce pain, disability, and the need for surgery.

Intra-articular injection of hyaluronan has been proposed as a means of restoring the normal viscoelasticity of the synovial fluid in patients with osteoarthritis and reducing pain and improving function. This treatment may also be called viscosupplementation. Hyaluronan is a naturally occurring macromolecule that is a major component of synovial fluid and is thought to contribute to its viscoelastic properties. Chemical crosslinking of hyaluronan increases its molecular weight; cross-linked hyaluronans are referred to as hylans. In osteoarthritis, the overall length of hyaluronan chains present in cartilage and the hyaluronan concentration in the synovial fluid are decreased.

REGULATORY STATUS

Several preparations of intra-articular hyaluronan have been approved by the U.S. Food and Drug Administration (FDA) as an alternative to nonsteroidal anti-inflammatory drug therapy in the treatment of osteoarthritis of the knee: Synvisc® and Synvisc-One® (Sanofi); GenVisc 850® (OrthogenRX); Gel-One® (Zimmer Biomet); Hyalgan® (Fidia Pharma); Supartz FX® (Bioventus); Orthovisc® (Anika); Euflexxa®, previously named Nuflexxa (Ferring); Monovisc® (Anika Therapeutics); Durolane® (Bioventus); GELSYN-3™ (Bioventus); Synojoynt™ (Arthrex); Hymovis® (Fidia Pharma); TriVisc® (OrthogenRX); Visco-3™ (Zimmer Biomet); and Triluron® (Fidia Pharma). Most products are manufactured from rooster combs, except for Durolane, Euflexxa, Orthovisc, Monovisc, Gel-Syn, Hymovis, TriVisc, and GenVisc 850, which are produced from bacterial fermentation. Also, Synvisc and other products undergo additional chemical crosslinking to create hylans with increased molecular weight (at least 6000 kDa) compared with

Hyalgan (500-730 kDa) and Supartz (620-1170 kDa). Monovisc is also cross-linked with a proprietary cross-linker. The differing molecular weights of the products lead to different half-lives; the half-life of Hyalgan or Supartz is estimated at 24 hours, while the half-life of Synvisc may range up to several days.

According to manufacturers' prescribing information for Synvisc and Euflexxa, intra-articular hyaluronan is "indicated for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy, and to simple analgesics, e.g., acetaminophen." The product inserts further indicate that Synvisc and Euflexxa should be injected intra-articularly into the knee joint once per week for a total of 3 injections over a 2- to 3-week period. In contrast, 5 weekly injections are recommended for the Hyalgan and Supartz products, and 3 to 4 weekly injections are recommended for Orthovisc. In 2009, the FDA approved the use of single-dose hylan G-F 20 (Synvisc-One) for the treatment of osteoarthritis of the knee. In 2011, the FDA approved the use of the single-dose cross-linked hyaluronate Gel-One (also known as Gel-200) for the treatment of osteoarthritis of the knee. In 2014, Monovisc was also approved as a single-dose treatment, while GELSYN-3 was approved as a course of 3 weekly injections. In 2015, GenVisc 850 was approved as a course of 3 weekly injections and Hymovis as a series of 2 injections one week apart. In 2017, Durolane was approved as a single-dose treatment and TriVisc as a course of 3 weekly injections. In 2018, Synojoynt and Visco-3 were approved as a course of 3 weekly injections. In 2019, Triluron was approved as a course of 3 weekly injections.

In 2000, the FDA approved removal of a precautionary statement from the package inserts for Hyalgan and Synvisc, which stated that the safety and efficacy of repeat courses had not been established.

FDA has not approved intra-articular hyaluronan for joints other than the knee.

FDA product code: MOZ.

POLICY

A. Intra-articular hyaluronan injections of the knee are considered **not medically necessary**.

B. Intra-articular hyaluronan injections are considered **experimental / investigational** for all other joints.

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.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through February 15, 2023.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

KNEE OSTEOARTHRITIS

Clinical Context and Therapy Purpose

The purpose of intra-articular hyaluronan injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as physical therapy, medication, and surgery, in individuals with osteoarthritis of the knee.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with osteoarthritis of the knee.

Interventions

The therapy being considered is intra-articular hyaluronan injections.

Intra-articular injection of hyaluronan into osteoarthritic joints is proposed to reduce pain and improve function. It is thought to replace endogenous hyaluronan and restore the viscoelastic properties of the synovial fluid.

Comparators

Comparators of interest include physical therapy, medication, surgery, and intra-articular corticosteroids. Medications used for treatment include nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, dietary supplements, and narcotics. Surgeries for osteoarthritis include arthroscopy (a procedure to diagnose and treat joint problems using a tiny camera inserted through a small surgical opening) and joint replacement.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, and treatment-related morbidity (Table 1).

Table 1. Outcomes of Interest for Individuals with Osteoarthritis of the Knee

Outcomes	Details
Symptoms	Pain, inflammation, limited range of motion, depression, or anxiety
Functional outcomes	Increased range of motion, increased mobility, and reduction of pain

The existing literature evaluating intra-articular hyaluronan injections as a treatment for osteoarthritis of the knee has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

This evidence review was informed by a TEC Assessment (1998) on intra-articular hyaluronan injections for osteoarthritis,[1,] and incorporated material from a 2004 and a 2014 TEC Assessment, and a 2007 TEC review for the Agency for Healthcare Research and Quality.[2,][3,][4,] The Agency for Healthcare Research and Quality (2007) report concluded that results from 42 RCTs generally showed positive effects of viscosupplementation on pain and function scores compared with placebo for patients with primary osteoarthritis of the knee.[4,] However, the evidence on viscosupplementation was accompanied by considerable uncertainty due to variable trial quality, potential publication bias, and unclear clinical significance of the changes reported. A 2016 protocol for an update of the Agency for Healthcare Research and Quality (2007) report does not include intra-articular hyaluronan because the technical expert panel concluded the evidence did not need updating.[5,]

The 2014 TEC Assessment involved a systematic review of recent meta-analyses on the treatment of knee osteoarthritis with intra-articular hyaluronan injections.[3,] Included in the evaluation were 5 meta-analyses published between 2011 and 2013.[6,7,8,9,10,] Two meta-analyses concluded that intra-articular hyaluronan provided a clinically meaningful benefit and 3 concluded that it did not, due to a lack of supportive evidence. It was not possible from the data to determine the proportions of patients achieving clinically meaningful improvement, although the analysis from the American Academy of Orthopaedic Surgeons determined that it was unlikely that an appreciable number of patients would benefit compared with placebo. It is also possible the results supporting a clinically meaningful benefit were biased in favor of intra-articular hyaluronan, due to unpublished trial data. When results from unpublished trials were obtained, the magnitude of treatment effect was notably lower compared with published results. Substantial heterogeneity between trials was also evident, increasing uncertainty. The TEC Assessment concluded the 5 meta-analyses, sampling from a similar collection of published trials and 2 unpublished ones, highlight biases and difficulty ascertaining clinically meaningful patient-level improvements compared with placebo. Although accumulating evidence would be expected to increase certainty of a clinically important treatment benefit, the studies evaluated did not provide convincing evidence that the net health outcome would improve with intra-articular hyaluronan over placebo.

A number of additional systematic reviews and meta-analyses have been published since the 2014 TEC Assessment.[11,12,13,14,15,16,17,18,19,20,21,] Some of these systematic reviews reported pooled analyses synthesizing results of RCTs that compared intra-articular hyaluronan with placebo, and reported the outcome, pain.[12,13,14,16,21,] Three of the new meta-analyses concluded that intra-articular hyaluronan injections for knee osteoarthritis provided a clinically meaningful reduction in pain compared with placebo.[13,14,16,] One meta-analysis (Jevsevar et al [2015][12,]) concluded that evidence from trials at low-risk of bias (e.g., double-blind, sham-controlled) did not demonstrate a clinically meaningful benefit of intra-articular hyaluronan. Two of the meta-analyses concluding benefit of intra-articular hyaluronan also limited analysis to trials at low-risk of bias. Two additional meta-analyses concluded that there was a small, statistically significant benefit, with clinical significance dependent on the threshold used.[11,20,]

As noted in the 2014 TEC Assessment, "....for a standardized mean difference, a minimally important difference of -0.37 is sometimes cited...."[Blue Cross and Blue Shield Association Technology.... ssments. 2014;Volume 29:Tab 6.][3,] The O'Hanlon (2016) meta-analysis of placebo-controlled, blinded trials found a standardized mean difference of -0.23.[20,] In contrast, the Johansen (2016) meta-analysis of placebo-controlled trials found a standardized mean difference of -0.39.[11,] However, when trials were stratified by risk of bias, the effect size of low-risk of bias trials was 0.0 and the effect sizes of the unclear and high-risk of bias trials were -0.81 and -0.35, respectively.[11,] Moreover, a stratified analysis by trial size found a standardized mean difference of -0.72, whereas trials with at least 100 patients showed a standardized mean difference of -0.21.

Conclusions that can be drawn from the newer meta-analyses are limited by potential biases with included trials. The presence of publication bias has been documented in the intra-articular hyaluronan literature.[6,] Likewise, a small trial bias has been noted with effect estimates from smaller trials (<100 participants) almost 3-fold that of large trials. These observations are consistent with positive results from a small trial having a higher probability of being reported than a small negative one (or possibly a small negative trial having even been completed). In fact, the O'Hanlon (2016) meta-analysis did identify a small trial bias; although there was an overall positive impact of intra-articular hyaluronan on pain, the effect size of small trials was much higher than that of large trials, and the effect size of large trials was below the level generally considered clinically significant.[20,] The results from the 2015 to 2016 meta-analyses (which did not include any new placebo-controlled randomized trials) do not alter conclusions of the 2014 TEC Assessment on the impact of intra-articular hyaluronan on health outcomes in patients with knee osteoarthritis.

Ran et al (2018) published a meta-analysis of studies comparing intra-articular hyaluronic acid and intra-articular methylprednisolone as treatments for knee osteoarthritis.[22,] Five RCTs published between 2003 and 2016 (N=1004; range, 60-433) were included. No significant difference was found between the 2 groups for Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores at 26 weeks (weighted mean difference= -0.073; 95% confidence interval [CI]: -0.46 to 0.314; p=.346), or for WOMAC physical function scores at 26 weeks (weighted mean difference= -0.031; 95% CI: -2.094 to 2.033; p=.977). The incidence of adverse effects, including nausea, vomiting, and headache, were also similar (risk difference= -0.042, 95% CI: -0.092 to 0.009; p=.107). The following limitations to the meta-analysis were reported: (1) only 5 studies were included, all with small sample sizes, (2) methodological weakness existed in all studies, (3) no subgroup analysis was performed, (4) studies only provided short-term follow-up, and (5) only English language studies were included.

Miller et al (2020) conducted a systematic review and meta-analysis of RCTs of intra-articular hyaluronan treatment compared to NSAIDs for knee osteoarthritis.[23,] Six studies were included (N=831), with a range of follow-up from 5 to 26 weeks. Hyaluronan injections were associated with statistically significant improvements in knee pain (standardized mean difference, 0.15; p=.04) and function (standardized mean difference [SMD], 0.23; p=.01) compared with NSAIDs, but these differences were small and not considered clinically important. The risk of overall adverse events was lower with intra-articular hyaluronan treatment than NSAIDs, but the incidence of serious adverse events, study withdrawal, and study withdrawal due to an adverse event did not differ between treatment groups. The most common potential sources of bias in

the included studies were a lack of information on blinding, industry funding, and incomplete outcome data.

Phillips et al (2020) published a systematic review and network meta-analysis comparing intra-articular high molecular weight hyaluronic acid, low molecular weight hyaluronic acid, standard-release corticosteroids, extended-release corticosteroids, platelet-rich plasma, and saline for knee osteoarthritis.[24,] Sixty-four studies were included representing 9710 patients. High molecular weight hyaluronic acid was the only treatment to surpass the minimally important difference for both pain (SMD, -0.53; 95% CI, -0.81 to -0.25) and function (SMD, -0.76; 95% CI. -1.30 to -0.22) when compared to placebo. High heterogeneity and inconsistency were noted for both pain and function network analyses ($I^2 \geq 90\%$).

Randomized Controlled Trials

Two RCTs from 2016 compared intra-articular hyaluronan with corticosteroid injection. Neither found a clinically meaningful benefit of intra-articular hyaluronan compared with corticosteroids. Limitations of both trials included lack of a placebo group, making conclusions about the efficacy of intra-articular hyaluronan compared with corticosteroids or placebo difficult to draw. Tammachote et al (2016) reported on a double-blind RCT in 110 patients with knee osteoarthritis.[25,] Patients received 1 injection of intra-articular hyaluronan (n=50) or corticosteroid (n=49) and were followed for 6 months. The primary outcome, pain at 6 months (measured by a 100-point visual analog scale), did not differ significantly between groups. Mean visual analog scale score at 6 months was 24 in the intra-articular hyaluronan group and 21 in the corticosteroid group (p>.05). At 1 week post injection, reported pain levels were significantly lower in the corticosteroid group (mean visual analog scale score, 14) than in the intra-articular hyaluronan group (mean visual analog scale score, 23; p=.018).

A RCT comparing intra-articular hyaluronan with corticosteroid injection in patients who had knee osteoarthritis was published by Askari et al (2016).[26,] Like the Tammachote (2016) study, it too, was double-blind and involved a single injection. Patients (N=140) were followed for 3 months, and pain was assessed using a 0- to 10-cm visual analog scale. At follow-up, there were no significant differences in pain scores between groups. Mean visual analog scale score at 3 months was 6.70 in the intra-articular hyaluronan group and 6.26 in the corticosteroid group (p=.720). After 1 month, mean pain score was significantly lower in the corticosteroid group (mean visual analog scale score, 5.59) than the intra-articular hyaluronan group (mean visual analog scale score, 6.63; p=.018).

The results of a multicenter RCT evaluating symptom modulation with amniotic suspension allograft injection compared with saline and hyaluronic acid was published by Farr et al (2019).[27,] A total of 200 patients were randomized 1:1:1 to each treatment group, with patients blinded to their allocation. Changes from baseline of patient-reported outcomes were monitored with the Knee Osteoarthritis Outcome Score and visual analog scale for pain. Patients reporting unacceptable pain at 3 month follow-up were considered treatment failures and were withdrawn from the study (13.2% amniotic suspension allograft; 68.8% hyaluronic acid; 75% placebo). At 3 and 6 months, the amniotic suspension allograft group had significantly greater improvements in mean Knee Osteoarthritis Outcome Score pain scores (3-mo: 11.69 [SD, 17.49]; 6-mo: 14.24 [19.96]) compared to both hyaluronic acid (3-mo: 6.27 [SD, 17.11]; 6-mo: 5.40 [15.84]) and saline (3-mo: 8.43 [SD, 16.87]; 6-mo: 7.38 [16.93]). Final response rates for amniotic

suspension allograft, hyaluronic acid, and saline groups were 69.1%, 39.1%, and 42.6% (p=.0007), respectively.

Hermans et al (2019) conducted an open-label RCT in individuals aged 18 to 65 years with symptomatic knee osteoarthritis (Kellgren and Lawrence I-III).[28,] Patients were randomized to non-surgical usual care and 3 weekly injections with high molecular weight hyaluronic acid (n=77) or usual care only (n=79). The primary outcome measure was the between group difference in responders per Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) criteria after 52 weeks, defined as at least 50% improvement from baseline and at least 20 mm absolute improvement from baseline on WOMAC visual analog scale pain subscore. The response rate based on pain during activity was 54.5% versus 34.2% (p=.015). The intervention group showed a statistically significant improvement based on individual response domains for pain during rest (p=.010), knee-related function (p=.010), and patient's global assessment (p<.0001). The study was limited by the lack of a placebo control.

Petterson et al (2019) published the results of a multicenter, double-blind RCT assessing the safety and effectiveness of lightly cross-linked hyaluronic acid (Monovisc; n=184; intent-to-treat=181) in the relief of joint pain in patients with idiopathic knee osteoarthritis compared to saline injection (n=185; intent-to-treat=184).[29,] A total of 331 patients (90%) completed the study through 6 months of follow-up. The primary effectiveness endpoint was defined as at least 50% improvement from baseline and at least 20 mm absolute improvement from baseline on WOMAC visual analog scale pain subscores. A clinically meaningful reduction in knee pain was observed in the hyaluronic acid versus saline group at 2 weeks (44.38 vs. 34.12; p<.001), 4 weeks (49.11 vs. 45.29; p=.003), and 6 months (51.14 vs. 48.97; p=.043). No clinically significant differences between groups were observed in the hyaluronic acid versus saline group at 8 weeks (55.03 vs. 50.00; p=.090), 12 weeks (52.53 vs. 52.63; p=.333), and 20 weeks (54.27 vs. 55.36; p=.835). No significant differences were detected between groups for any secondary endpoint measures of individual response domains.

Section Summary: Knee Osteoarthritis
In regard to the treatment of knee osteoarthritis, many RCTs have been published over the last 2 decades. While the outcomes of these RCTs have been mixed, the RCT evidence base is characterized by studies showing small treatment effects of intra-articular hyaluronan treatment. In many cases, these trials are at risk of bias, and it cannot be determined with certainty whether there is a true treatment effect or whether the reported differences are due to bias. Meta-analyses of RCTs have also had mixed findings. Some meta-analyses, estimating the magnitude of treatment benefit, have concluded there is no clinically significant benefit; others have concluded there is a clinically significant benefit. These meta-analyses have also highlighted the limitations of this evidence base, most notably publication bias and small trial bias. For example, a 2016 meta-analysis found more than a 3-fold larger treatment effect in smaller trials than in larger trials (i.e., >100 participants). Overall, given the lack of a definitive treatment benefit despite a large quantity of literature, and given the biases present in the available evidence, it is unlikely there is a clinically meaningful treatment benefit.

OSTEOARTHRITIS OF JOINTS OTHER THAN THE KNEE

Clinical Context and Therapy Purpose

The purpose of intra-articular hyaluronan injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as physical therapy, medication, and surgery, in individuals with osteoarthritis of joints other than the knee.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with osteoarthritis of joints other than the knee.

Interventions

The therapy being considered is intra-articular hyaluronan injections.

Intra-articular injection of hyaluronan into osteoarthritic joints is proposed to reduce pain and improve function. It is thought to replace endogenous hyaluronan and restore the viscoelastic properties of the synovial fluid.

Comparators

Comparators of interest include physical therapy, medication, surgery, and intra-articular corticosteroids. Medications used for treatment include NSAIDs, analgesics, dietary supplements, and narcotics. Surgeries for osteoarthritis include arthroscopy (a procedure to diagnose and treat joint problems using a tiny camera inserted through a small surgical opening) and joint replacement.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, and treatment-related morbidity (Table 2).

Table 2. Outcomes of Interest for Individuals with Osteoarthritis of Joints Other than the Knee

Outcomes	Details
Symptoms	Pain, inflammation, limited range of motion, depression, or anxiety
Functional outcomes	Increased range of motion, increased mobility, and reduction of pain

The existing literature evaluating intra-articular hyaluronan injections as a treatment for osteoarthritis of joints other than the knee has varying lengths of follow-up, ranging from 3 months to 2 years. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 2 years of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

3. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

ANKLE OSTEOARTHRITIS

Systematic Reviews

Vannabouathong et al (2018) published a systematic review of intra-articular injections for the treatment of ankle osteoarthritis.[30,] A total of 27 studies were identified (N=1085), including 20 observational studies and 7 small RCTs evaluating hyaluronic acid conducted between 2005 and 2014. Pooled analysis (3 RCTs, 109 patients) demonstrated significantly improved Ankle Osteoarthritis Scale scores with hyaluronic acid compared to saline at 6 months (mean difference 12.47 points; 95% CI, 1.18 to 23.77; p=.03). Study heterogeneity was low (I^2 = 0%; p=.41).

A Cochrane review by Witteveen et al (2015) addressed intra-articular hyaluronan and other conservative treatments for ankle osteoarthritis.[31,] Reviewers identified 6 RCTs, 3 of which were double-blind and compared intra-articular hyaluronan with placebo. The other trials were single-blind. Two of them compared intra-articular hyaluronan with another treatment (exercise in 1 study, botulinum toxin in the other) and the sixth trial compared different doses of hyaluronan. Five of the 6 trials included patients with unilateral ankle pain. Sample sizes at randomization ranged from 17 to 75, and length of follow-up ranged from 3 to 12 months. The authors pooled findings only for 2 of the 3 studies comparing intra-articular hyaluronan with placebo. Meta-analyses of efficacy outcomes (pain, function) did not find a statistically significant benefit favoring intra-articular hyaluronan over placebo, with the exception of the outcome Ankle Osteoarthritis Scale total score at 6 months. For the Ankle Osteoarthritis Scale outcome, the pooled effect size was -12.53 (95% CI, -23.84 to -1.22) in favor of intra-articular hyaluronan; however, the evidence for this analysis was rated as low due to the limitation in study design (i.e., unclear risk of bias) and "…imprecision of result (low number of participants)." No serious adverse events were reported and no patient withdrew from the trial due to an adverse event.

Migliore et al (2011), in a review on intra-articular hyaluronan for ankle osteoarthritis, considered RCTs and observational studies.[32,] They identified 3 small RCTs with a total of 75 patients, and 4 case series. In 2 of the RCTs, intra-articular hyaluronan was compared with placebo injection and the third RCT compared intra-articular hyaluronan with exercise therapy. Reviewers were unable to conduct a meta-analysis due to the limited number of studies and study heterogeneity.

FOOT OSTEOARTHRITIS

Randomized Controlled Trials

There is a very limited amount of evidence on intra-articular hyaluronan injections in the foot. Munteanu et al (2011) reported on an RCT of a single intra-articular hyaluronan injection in 151 patients with first metatarsophalangeal joint osteoarthritis.[33,] At the 1-, 3-, and 6-month follow-ups, there were no significant differences between the intra-articular hyaluronan and placebo groups on the Foot Health Status Questionnaire.

THUMB OR HAND OSTEOARTHRITIS

Systematic Reviews

Three systematic reviews have evaluated intra-articular hyaluronan and corticosteroid injections for treating thumb osteoarthritis. Kroon et al (2016) identified 3 studies comparing intra-articular hyaluronan with placebo and 6 comparing intra-articular hyaluronan and corticosteroids.[34,] Findings from the intra-articular hyaluronan studies were not pooled.

A systematic review by Trellu et al (2015) included only RCTs and pooled study data.[35,] Six trials (N=428) were included in the meta-analyses; 169 patients were treated with hyaluronan , 147 with corticosteroids, and 74 with placebo. In a pooled analyses of trials comparing intra-articular hyaluronan with placebo (74 patients in each arm), there was no significant between-group difference in pain at week 12 (standardized response mean, -0.95; 95% CI, -3.87 to 1.97); however, functional capacity at week 12 was significantly better after intra-articular hyaluronan than after placebo (standardized response mean, -1.14; 95% CI, -1.69 to -0.60). When intra-articular hyaluronan and corticosteroids were compared, there were no significant differences in pain, functional capacity, or pulp pinch force at 12 weeks. At 24 weeks, findings were mixed. There was no significant difference between intra-articular hyaluronan and corticosteroids in functional capacity, intra-articular hyaluronan was superior on pulp pinch force status (standardized response mean, -1.66; 95% CI, -0.75 to -2.57), and corticosteroids were superior on pain (standardized response mean, 1.44; 95% CI, 0.14 to 2.74).

Riley et al (2019) conducted a systematic review of injection therapies for base of thumb osteoarthritis.[36,] Meta-analysis of 2 RCTs that compared corticosteroid injections to intra-articular hyaluronan (92 patients) demonstrated reduced visual analogue scale pain on activity with corticosteroid versus intra-articular hyaluronan (mean difference [MD], −1.32; 95% CI, −2.23 to −0.41) in the medium term (3 to 6 months), but no differences in other measures of pain or function in the short term (1 week to 3 months) or long term (longer than 6 months).

In another systematic review, Kroon et al (2018) updated the evidence on the efficacy and safety on non-pharmacological, pharmacological, and surgical interventions for hand osteoarthritis with a systematic literature review through 2017.[37,] No clear beneficial effect was shown for intra-articular thumb base injections of hyaluronic acid. This evidence review informed the 2018 update of the European League Against Rheumatism management recommendations for hand osteoarthritis.

HIP OSTEOARTHRITIS

Systematic Reviews

A systematic review by Lieberman et al (2015) included RCTs and observational studies (with a minimum of 10 patients) evaluating intra-articular hyaluronan for treatment of pain associated with hip osteoarthritis.[38,] Twenty-three studies were identified, 6 of which were RCTs. The studies evaluated 11 different formulations of intra-articular hyaluronan. Durations of follow-up varied; 19 studies followed patients for 6 months or less, 3 studies had between 6 months and 1 year of follow-up, and 1 study followed patients for more than 1 year. The primary efficacy outcome was change from baseline in pain measured by a visual analog scale. Reviewers did not report the number of points on the visual analog scale, but presumably this differed across studies and reviewers appeared to standardize results on a 10-point visual analog scale. A pooled analysis of data from all studies found a statistically significantly lower pain score at follow-up compared

with baseline. Mean change was -1.97 points on the visual analog scale (95% CI, -2.83 to -1.12). In a pooled analysis of the 6 RCTs, there was a significantly greater decrease in pain with intra-articular hyaluronan than with a control intervention (-0.27 points on a visual analog scale; 95% CI, -0.43 to -0.11). Although statistically significant, a between-group difference of 0.27 points on a visual analog scale may not be clinically meaningful.

Wu et al (2017) published a meta-analysis of RCTs investigating the therapeutic effects of hyaluronan injections in patients with hip osteoarthritis.[39,] Six studies were selected. To measure the effects of hyaluronan injection, a series of pain and functionality assessments were conducted using a visual analog scale, the Lequesne Index, and the WOMAC. All 6 trials consisted of 2 treatment groups (hyaluronan vs. control). Follow-up ranged from 52 to 180 days. When comparing hyaluronan with control, the pooled effect size of improvement in pain scores was 0.03 (95% CI, -0.20 to 0.26; $p<.05$). The standardized mean difference for improvement in Lequesne Index scores and WOMAC scores were -0.24 (95% CI, -0.50 to 0.02; $p>.05$) and -0.13 (95% CI, -0.64 to 0.37; $p>.05$), respectively. Reviewers noted there were likely no significant differences between hyaluronan injections and saline or other treatments. Limitations included the small sizes of selected studies, selection bias, and expectation bias.

Zhao et al (2020) published a systematic review and meta-analysis evaluating various intra-articular injections for hip osteoarthritis, including platelet-rich plasma, hyaluronic acid, corticosteroids, and hyaluronic acid with platelet-rich plasma.[40,] A literature review through April 2018 was performed identifying 11 RCTs, representing 1060 patients. Mean follow-up duration ranged from 3 to 12 months. Studies varied with regard to imaging method used for guidance (ultrasound vs. fluoroscopy). A pair-wise meta-analysis indicated that corticosteroids and hyaluronic acid were superior to control in reducing visual analog scale score at 1 and 3 months ($p<.05$) and that a corticosteroid injection was superior to hyaluronic acid in reducing visual analog scale score at 1 month ($p<.05$). The authors recommend corticosteroid injections as the most efficient agent for hip osteoarthritis in the short-term.

A systematic review and meta-analysis by Liao et al (2019) included 5 high quality RCTs representing 591 patients with hip osteoarthritis treated with intra-articular viscosupplementation.[41,] Although several trials demonstrated a significant decrease in visual analog scale pain scores from baseline, meta-analysis did not indicate viscosupplementation was superior to placebo at follow-up time windows of 7 to 14 days, 28 to 30 days, or final visit.

Gazendam et al (2021) published a systematic review and network meta-analysis of RCTs investigating the efficacy of intra-articular corticosteroid, hyaluronic acid, and platelet-rich plasma injections for the treatment of hip osteoarthritis.[42,] A literature search through 2019 identified 11 studies for inclusion, representing 1353 patients. For both pain and functional outcomes at 2 to 4 and 6 months, none of the interventions significantly outperformed intra-articular saline injections. All interventions (including placebo) led to a clinically important improvement in pain and function from baseline, except for the combination of hyaluronic acid and platelet-rich plasma.

Systematic review characteristics and results are summarized in Tables 3 and 4.

Table 3. Hip Osteoarthritis Systematic Reviews and Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Lieberman (2015)[38,]	2002-2011	23	Patients with hip OA	3868 (12-2343)	RCT, Retrospective, Prospective	NR
Wu (2017)[39,]	2005-2010	6	Patients with hip OA	NR	RCT	NR
Zhao (2019)[40,]	2004-2017	11	Patients with hip OA	1060 (43-305)	RCT	3-12 mo
Liao (2019)[41,]	2006-2018	5	Patients with hip OA	591 (42-357)	RCT	3-6 mo
Gazendam (2021)[42,]	Through 2019	11	Patients with hip OA	1353 (43-357)	RCT	2-6 mo

OA: osteoarthritis; NR: not reported; RCT: randomized controlled trial.

Table 4. Hip Osteoarthritis Systematic Reviews and Meta-Analysis Results

Study	Decrease in VAS	Difference in Pooled Lequesne Index (SMD)	Difference in WOMAC Scores (SMD)
Lieberman (2015)[38,]	-1.97[a]		
95% CI	-2. 83 to -1.12		
p-value	<.001		
Wu (2017)[39,]	-0.72[b]	-0.74	-7.75
95% CI	-1.06 to -0.39	-1.42 to -0.51	-14.28 to -1.21
p-value	<.05	<.05	<.05
Zhao (2019)[40,]	HA: -1.16[b] CS: -1.16[b]		0.71[c]
95% CI	HA: -2.35 to -0.85 CS: -2.35 to -0.52		-4.03 to 5.45
p-value	HA:.039, I^2=0% CS:.043, I^2=79.4%		.770, I^2=98.6%
Liao (2019)[41,]	-0.14[b]		-0.28[b,d]
95% CI	-0.46 to 0.18		-0.60 to 0.05
p-value	.38; I^2=63%		.10; I^2=63%
Gazendam (2021)[42,]	-1.1[b,e]		-2.42[b,e]
95% CI	-2.9 to 0.64		-11.5 to 5.53
p-value	NR		NR

CI: confidence interval; CS: corticosteroid; HA: hyaluronic acid; SMD: standard mean difference; VAS: visual analog score; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
[a] Compared to baseline.
[b] Compared to placebo control.

[c] Compared to corticosteroid.
[d] Standard mean difference based on WOMAC or Lequesne Index scores.
[e] Mean difference at 2-4 months.

SHOULDER OSTEOARTHRITIS

Systematic Reviews

Colen et al (2014), in a systematic review, identified RCTs, controlled observational studies, and case series evaluating intra-articular hyaluronan for treatment of glenohumeral osteoarthritis in adults.[43,] Eight studies met the eligibility criteria; 2 were RCTs, 5 were prospective case series, and 1 was a retrospective case-control study. Due to heterogeneity across studies and the small number of controlled studies, reviewers did not pool study findings on the efficacy of intra-articular hyaluronan versus placebo or an alternative intervention for treating shoulder osteoarthritis.

Zhang et al (2019) published a systematic review and meta-analysis of studies of intra-articular hyaluronan for treatment of glenohumeral osteoarthritis that found reductions in pain and functional outcomes at 3 and 6 months with intra-articular hyaluronan treatment.[44,] However, similar clinical improvements were seen in control groups, suggesting a significant placebo effect. The reviewers concluded that further RCTs are necessary to evaluate efficacy of the treatment.

Randomized Controlled Trials

Blaine et al (2008) was an industry-sponsored trial; it had 3 arms with 660 patients who had persistent shoulder pain due to glenohumeral joint osteoarthritis, rotator cuff tear, and/or adhesive capsulitis, and compared 3 weekly with 5 weekly injections of sodium hyaluronate (Hyalgan) with 5 weekly injections of saline.[45,] Approximately 60% of patients had osteoarthritis, although most with osteoarthritis also had rotator cuff disorders or capsulitis. Sixty-nine percent (n=456) of the patients had a follow-up visit at 26 weeks. There was no significant difference among groups in the primary outcome measure (shoulder pain with movement at 13 weeks). Analysis of predefined, stratified subgroups revealed no significant differences in reported pain at 13 weeks. However, a statistically significant decrease of 7.5 mm and 7.8 mm (on a 100-mm visual analog scale) in reported pain in both treatment groups at 26 weeks compared with placebo was seen among patients with osteoarthritis. In those without osteoarthritis, there were no significant improvements with either regimen. Of note, this appears to be an as-treated analysis of the osteoarthritis subgroup data, and the difference may not be clinically meaningful.

Kwon et al (2013) published findings from a multicenter, randomized, double-blind, placebo-controlled trial of intra-articular hyaluronan in 300 patients with glenohumeral osteoarthritis.[46,] Intention-to-treat analysis found similar improvements from baseline in 100-mm visual analog scale for pain (19.88 mm for intra-articular hyaluronan, 16.29 mm for sham treatment) and in the Outcome Measures in Rheumatoid Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) high responder rate (40.8% for intra-articular hyaluronan, 34.9% for sham) at 26 weeks. In a subset of intra-articular hyaluronan patients, there were statistically significant differences of 4.0 mm in visual analog scale score and 8.37% on the OMERACT-OARSI. However, the clinical significance of these differences is uncertain.

Trial characteristics and results are summarized in Table 5 and 6. Study relevance, design, and conduct limitations are summarized in Table 7 and 8.

Table 5. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions		
					Active	***Comparator (1)***	***Comparator (2)***
Blaine (2008)[45],	U.S.	79	NR	Patients with glenohumeral joint OA	Five weekly 2-mL injections of sodium hyaluronate (n=221)	Three weekly injections of sodium hyaluronate followed by 2 weekly injections of phosphate-buffered saline solution (n=218)	Five weekly 2-mL injections of phosphate-buffered saline solution (n=221)
Kwon (2013)[46],	U.S.	23	NR	Patients with glenohumeral OA	Three weekly injections of sodium hyaluronate (n=150)	Three weekly injections of phosphate-buffered saline (n=150)	

NR: not reported; OA: osteoarthritis; RCT: randomized controlled trial; U.S.: United States.

Table 6. Summary of Key RCT Results

Study	Mean VAS Reduction from Baseline to 13 Wk	Mean VAS Improvement from Baseline to 26 Wk	Rate of Any AE	Rate of Serious AE
Blaine (2008)[45],				
5-Injection	26.4±1.8			
3-Injection	26.3±1.8			
Control	23.0±1.8			
Kwon (2013)[46],				
HA		19.88 mm	56.7%	7.3%
Control		16.29 mm	66.0%	3.3%
p-value			.1231	.1977

AE: adverse event; HA: sodium hyaluronate; RCT: randomized controlled trial; VAS: visual analog score.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Blaine (2008)[45,]		3. Investigators had different levels of experience with the injections			
Kwon (2013)[46,]		3. Ultrasound or fluoroscopic guidance for injection was only used at the discretion of the investigators			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow-Up[d]	Power[e]	Statistical[f]
Blaine (2008)[45,]	1. Randomization process not described 3. Allocation concealment unclear	1,2,3. Blinding not described		1. Only 69.1% of participants completed all 26 weeks of follow-up		
Kwon (2013)[46,]	1. Randomization process not described					3. p-values and confidence intervals not reported for all results

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4.

Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Spine Osteoarthritis
The data are limited to small pilot studies and case series.

Section Summary: Osteoarthritis in Joints Other Than the Knee
The evidence for use of intra-articular hyaluronan in joints other than the knee includes RCTs and systematic reviews for treating the ankle, foot, thumb, hip, and shoulder. Meta-analyses of RCTs either have not found statistically significant benefits of the procedure on health outcomes or have found benefits that were statistically, but likely not clinically, significant (e.g., 0.27-point improvement on a 10-point visual analog scale for studies on hip osteoarthritis). There were fewer published studies on treating foot joints and spine osteoarthritis.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2011 Input
In response to requests, input was received from 5 academic medical centers (6 reviewers) and 3 physician specialty societies while this policy was under review in 2011. Most reviewers agreed that intra-articular hyaluronan of the knee was medically necessary. In addition, those providing input supported an interval of 6 months for repeat injections. In response to a question about total number of treatment courses, there was no consensus.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Medical Society for Sport Medicine
In 2016, the scientific statement from the American Medical Society for Sport Medicine recommended intra-articular hyaluronan for "appropriate" patients with knee osteoarthritis based on high-quality evidence.[14,] Patient selection criteria included individuals age 60 and older with Kellgren-Lawrence grade 2 or 3 osteoarthritis. The Society also "suggests" intra-articular

hyaluronan for patients under age 60 with knee osteoarthritis based on moderate-quality indirect evidence.

American Academy of Orthopaedic Surgeons
In 2021, the guidelines from the American Academy of Orthopaedic Surgeons (AAOS) on treatment of osteoarthritis of the knee indicated that AAOS does not recommend routine use of intra-articular hyaluronic acid for patients with symptomatic knee osteoarthritis.[47,] This recommendation was moderate. It was based on a meta-analysis of 28 studies that showed the overall effect was less than 0.5 minimally important different units, indicating a low likelihood that an appreciable number of patients achieved clinically important benefits. These guidelines replaced 2013 guidelines, which included a strong recommendation against use of intra-articular hyaluronic acid.

In 2017, the AAOS clinical practice guidelines on hip osteoarthritis included a recommendation that intra-articular hyaluronic acid could not be recommended in patients with symptomatic hip osteoarthritis, because it was not better than a placebo.[48,] This was based on strong evidence as assessed in 8 high-quality studies that evaluated intra-articular hyaluronan against corticosteroids and placebo. Several studies showed no difference in patient pain and function after treatment with intra-articular hyaluronan against placebo. Studies reviewing different formulations of intra-articular hyaluronan were also considered.

In 2009 (reaffirmed in 2014), the AAOS clinical practice guidelines on glenohumeral joint osteoarthritis included a weak grade C recommendation that the "use of injectable viscosupplementation is an option when treating patients with glenohumeral [shoulder] osteoarthritis."[49,] Grade C recommendations are based on poor-quality evidence. In this instance, the recommendation was based on a single case series of 30 patients with osteoarthritis of the glenohumeral joint who received 3, weekly intra-articular injections of hylan G-F 20 (Synvisc).[50,] At 1, 3, and 6 months, clinically significant improvements were seen in pain, function, and quality of life measures. In 2020, the updated AAOS clinical practice guidelines stated that "strong evidence supports that there is no benefit in the use of hyaluronic acid in the treatment of glenohumeral joint osteoarthritis."[51,]

American College of Rheumatology
In 2019, the American College of Rheumatology updated its guidelines on osteoarthritis of the hand, hip, and knee.[52,] A conditional recommendation against the use of intra-articular hyaluronic acid was given for the treatment of osteoarthritis of the knee and first carpometacarpal joint of the hand. The College also made a strong recommendation against the use of intra-articular hyaluronic acid for the treatment of osteoarthritis of the hip. These recommendations were informed by a review indicating that the effect size of hyaluronic acid injections compared to saline injections approaches 0 when analysis is limited to trials with low risk of bias. While the evidence of lack of benefit is higher quality for the hip, the conditional recommendation for osteoarthritis of the knee and hand was made in the context of clinical shared decision-making that recognizes the treatment may provide benefit when alternatives have failed to provide benefit and have been exhausted.

Osteoarthritis Research Society International
In 2014, the Osteoarthritis Research Society International (OARSI) guidelines, developed by consensus after review of existing guidelines and systematic reviews, gave an "uncertain"

recommendation for the use of intra-articular hyaluronan for knee osteoarthritis and a recommendation of "not appropriate" for multijoint osteoarthritis.[53,]

In 2019, OARSI updated these guidelines, as derived from expert consensus and review of high-quality meta-analytic data. Intra-articular hyaluronic acid was conditionally recommended for the treatment of knee osteoarthritis for longer term treatment effect, as it was associated with symptom improvement beyond 12 weeks with a favorable safety profile. This recommendation was provided with high consensus for patients with comorbidities (e.g., gastrointestinal, cardiovascular, frailty). This recommendation was provided with low consensus for patients with no comorbidities. The use of hyaluronic acid for the treatment of hip or polyarticular osteoarthritis was not recommended.[54,]

National Institute for Health and Care Excellence
In 2022 , the clinical guideline issued by the National Institute for Health and Care Excellence for osteoarthritis diagnosis and management stated: "Do not offer intra-articular hyaluronan injections to manage osteoarthritis."[55,]

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05492851	A Double-blind, Randomized Trial Comparing Three Single Dose Injections for Knee Osteoarthritis	165	Aug 2024
Unpublished			
NCT04231318	A Randomized, Double-Blind, Placebo Controlled, Multi-Center Study of a Single Injection Cross-Linked Sodium Hyaluronate Combined With Triamcinolone Hexacetonide (Cingal®) to Provide Symptomatic Relief of Osteoarthritis of the Knee	231	May 2022
NCT04204265[a]	A Prospective Study of a Single Injection Cross-linked Sodium Hyaluronate (MONOVISC) to Provide Symptomatic Relief of Osteoarthritis of Shoulder Joint	25	Mar 2021 (completed)
NCT04204278[a]	A Prospective Study of a Single Injection Cross-linked Sodium Hyaluronate (MONOVISC) to Provide Symptomatic Relief of Osteoarthritis of Ankle Joint	25	Mar 2021 (completed)
NCT04204083[a]	A Prospective Study of a Single Injection Cross-linked Sodium Hyaluronate (MONOVISC) to Provide Symptomatic Relief of Osteoarthritis of Hip Joint	25	Mar 2021 (completed)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
J7318	Hyaluronan or derivative, durolane, for intra-articular injection, 1 mg
J7320	Hyaluronan or derivative, Genvisc 850, for intra-articular injection, 1 mg
J7321	Hyaluronan or derivative, Hyalgan, Supartz or Visco-3, 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-3, 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

REVISIONS	
01-01-2007	Added HCPCS Codes: Q4083, Q4084, Q4085, Q4086
03-31-2007	Deleted HCPCS Code: J7319
12-31-2007	Deleted HCPCS Codes: Q4083, Q4084, Q4085, Q4086
01-01-2008	Added HCPCS Codes: J7321, J7322, J7323, J7324.
12-24-2008	In Description: ▪ Revised wording from "…intra-articular lubricants in patients with any musculoskeletal condition, including osteoarthritis." To "…intra-articular lubricants in patients with osteoarthritis of the knee." In Policy section: ▪ Added "The use of hyaluronan injections may be considered medically necessary when all of the following are met:" ahead of the three criteria.
01-01-2010	In Coding Section: ▪ Added HCPCS Code: J7325 ▪ Removed HPCS Code: J7322
	In Policy Section / Utilization: ▪ Added: "Synvisc-One is a single injection treatment regimen"
01-01-2012	In the Coding section: ▪ Added HCPCS code: J7326

REVISIONS	
09-24-2012	In the Policy Title, removed "of the Knee" to read "Intra-articular Hyaluronan Injections for Osteoarthritis"
	Description section updated.
	Added Medical Policy and Coding Disclaimers.
	In the Policy section: ▪ Revised the following policy language: The use of hyaluronan injections may be considered medically necessary when all of the following are met: 1. Diagnosis of Osteoarthritis (degenerative arthritis) for knee only. 2. Failed conservative treatment, i.e., anti-inflammatory agents, physical therapy, weight loss, activity modification, knee brace, and occasional corticosteroid injection. Reconstructive surgery where a knee is unstable and surgery is indicated. 3. The series of injections (one course) can be repeated every six months. ▪ In the Utilization portion, added: • Euflexxa® is a 3-5 dose course of treatments. • Gel One ® is a 3-5 dose course of treatments. • Orthovisc ® is a 3-5 dose course of treatments.
	Added Rationale section.
	Updated Reference section.
10-26-2012	In the Policy section: ▪ In the Utilization section, removed the 4th bullet, "Gel One ® is a 3-5 dose course of treatments." ▪ In the Utilization section, last sentence, added "® and Gel-One ® are" and removed "is" to read "Synvisc-One ® and Gel-One ® are a single injection treatment regimen."
10-01-2013	Updated Description section.
	In Policy section: ▪ Revised the following medical policy language: "A. Intra-articular hyaluronan injections may be considered medically necessary for treatment of painful osteoarthritis of the knee in patients who have insufficient pain relief from conservative nonpharmacologic therapy and simple analgesics. B. Repeated courses of intra-articular hyaluronan injections of the knee may be considered medically necessary under the following conditions: • Significant pain relief achieved with the prior course of injections; and • At least 6 months have passed since completion of the prior course. C. The use of intra-articular hyaluronan injections in joints other than the knee is considered experimental / investigational." ▪ Removed "Utilization" section. ▪ Added "FDA Approved Indications and Dosage" table.
	In Coding section: ▪ Added ICD-10 Diagnosis codes. *(Effective October 1, 2014)*
	Updated Rationale section.
	Updated Reference section.
05-01-2014	In Title section: ▪ Removed links to Prior Authorization information and Drug Formulary.
	Updated Description section.
	In Policy section: ▪ Changed the current medical policy language From:

REVISIONS	
	"A. *Preferred* Viscosupplements may be considered medically necessary when ALL the following are met: 1. The patient has a diagnosis of OA of the knee AND 2. The patient has tried and failed to respond adequately to conservative nonpharmacologic therapy AND to simple analgesics [acetaminophen or NSAIDs] AND 3. ONE of the following: a. The patient is receiving his/her first course of viscosupplement OR b. the patient's previous course of viscosupplement was at least 6 months previous OR c. the request is for the other knee joint not previously treated AND 4. The dose of the requested agent is within FDA labeled dosing guidelines. B. *Non-preferred* Viscosupplements may be considered medically necessary when all of the following are met: 1. The patient has a diagnosis of OA of the knee AND 2. The patient has tried and failed to respond adequately to conservative nonpharmacologic therapy AND simple analgesics [acetaminophen or NSAIDs] AND 3. ONE of the following: a. The patient has evidence of use of the preferred agent in pharmacy claims or medical history at least 6 months prior to request of the non-preferred agent OR b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred viscosupplement agent. AND 4. It has been at least 6 months since the patient used the preferred agent OR any other viscosupplement for the same knee joint AND 5. The dose of the requested agent is within FDA labeled dosing guidelines C. Repeated courses of intra-articular hyaluronan injections of the knee may be considered medically necessary under the following conditions: 1. Significant pain relief achieved with the prior course of injections; AND 2. At least 6 months have passed since completion of the prior course. D. The use of intra-articular hyaluronan in the knee when the above criteria are not met, and injections in joints other than the knee is considered experimental / investigational." To: "Intra-articular hyaluronan injections are considered not medically necessary."
	Updated Rationale section.
	In Coding section: ▪ Removed Diagnoses codes
	Updated Reference section.
01-01-2016	In Coding section: ▪ Added HCPCS codes: J7328, Q9980.
	Updated References section.
04-01-2016	In Coding section: ▪ Added HCPCS code: C9471.
07-22-2016	Updated Description section.
	In Policy section: ▪ In Item A, added "of the knee" to read "Intra-articular hyaluronan injections of the knee are considered not medically necessary." ▪ Added Item B, "Intra-articular hyaluronan injections are considered experimental / investigational for all other joints.
	Updated Rationale section.
	Updated References section.
01-01-2017	In Coding section:

REVISIONS	
	▪ Added HCPCS codes: J7320, J7322 *(New codes, effective January 1, 2017)*.
05-24-2017	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Added HCPCS code: J7327. ▪ Removed HCPCS codes: Q9980, C9471.
	Updated References section.
01-01-2018	In Coding section: ▪ Revised nomenclature to HCPCS code: J7321.
05-23-2018	Updated Description section.
	Updated Rationale section.
	Updated References section.
01-01-2019	In Coding section: ▪ Added new HCPCS codes: J7318, J7329.
05-21-2019	Updated Description section.
	Updated Rationale section.
	Updated References section.
10-01-2019	In Coding section: ▪ Added HCPCS Codes: J7331, J7332
04-19-2021	Updated Description section.
	Updated Rationale section.
	Updated References section.
05-20-2022	Updated Description Section
	Updated Rationale Section
	Updated References Section
05-23-2023	Updated Description Section
	Updated Rationale Section
	Updated References Section

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