Medical Policy

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Title: Intra-Articular Hyaluronan Injections for Osteoarthritis

Professional
Original Effective Date: January 2001
Revision Date(s): April 11, 2001; May 1, 2002; June 12, 2002; April 7, 2006; May 19, 2006; January 9, 2007; April 19, 2007; July 1, 2007; December 31, 2007; January 1, 2008; January 1, 2010; January 1, 2012; September 24, 2012; October 26, 2012; October 1, 2013; May 1, 2014; January 1, 2016; April 1, 2016; July 22, 2016; January 1, 2017; May 24, 2017; January 1, 2018; May 23, 2018; January 1, 2019; May 21, 2019; October 1, 2019; April 19, 2021
Current Effective Date: July 22, 2016

Institutional
Original Effective Date: July 1, 2007
Revision Date(s): December 31, 2007; January 1, 2008; January 1, 2010; January 1, 2012; September 24, 2012; October 26, 2012; October 1, 2013; May 1, 2014; January 1, 2016; April 1, 2016; July 22, 2016; January 1, 2017; May 24, 2017; January 1, 2018; May 23, 2018; January 1, 2019; May 21, 2019; October 1, 2019; April 19, 2021
Current Effective Date: July 22, 2016

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	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	Relevant outcomes include: • Symptoms • Functional outcomes • Treatment-related morbidity

DESCRIPTION

Intra-articular (IA) 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 (OA), and this is the U.S. Food and Drug Administration-approved indication. Other joints, such as the hip and shoulder, are being investigated for IA hyaluronan treatment of OA.

OBJECTIVE

The objective of this evidence review is to determine whether intra-articular injection of hyaluronan improves the net health outcome in patients 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® (Genzyme); Gel-One® (Zimmer); Hyalgan® (Fidia); Supartz FX™ (Bioventus); Orthovisc® (Anika); Euflexxa®, previously named Nuflexxa (Savient); Monovisc® (Anika Therapeutics); Durolane® (Bioventus); and Gel-Syn™ (Institut Biochimique SA). All products are manufactured from rooster combs, except for Durolane®, Euflexxa®, Orthovisc®, Monovisc®, Gel-Syn™, and GenVisc 850, which are produced from bacterial fermentation. Also, Synvisc® undergoes additional chemical crosslinking to create hylans with increased molecular weight (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 three injections over a 2- to 3-week period. In contrast, five weekly injections are recommended for the Hyalgan® and Supartz™ products, and three to four 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 Gel-Syn™ was approved as a course of 3 weekly injections. In 2015, GenVisc 850 was approved as a course of 3 weekly injections. In 2017, Durolane was approved as a single-dose treatment.

In 2000, the FDA approved removal of a precautionary statement from the package inserts for Hyalgan® and Synvisc®, which indicated that 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.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through January 30, 2020.

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 function¾including 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, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one 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. RCTs 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.

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 patients with osteoarthritis of the knee.

The question addressed in this evidence review is: Does intra-articular injection of hyaluronan improve the net health outcome in patients with osteoarthritis of the knee and other joints (e.g., hip, shoulder)?

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

Patients

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.

Patients with osteoarthritis of the knee are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

Comparators
Comparators of interest include physical therapy, medication, and surgery. Medications used for treatment include nonsteroidal anti-inflammatory drugs, 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. All of the comparators of interest are managed by physical therapists, orthopedic surgeons, and primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, and treatment-related morbidity.

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 one 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.

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 three 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 is was unlikely that an appreciable number of patients would benefit compared with placebo.[7] 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 five meta-analyses, sampling from a similar collection of published trials and two 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] 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] 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, and clinical significance depends 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...."[3] The O'Hanlon (2016) meta-analysis of placebo-controlled, blinded trials found an standardized mean difference of -0.23.[20] In contrast, the Johansen (2016) meta-analysis of placebo-controlled trials found an 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 an standardized mean difference of -0.72, whereas trials with at least 100 patients showed an 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 2015-2016 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.[21,] Five RCTs published between 2003 and 2016, and 1004 total patients (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=0.346), or for WOMAC physical function scores at 26 weeks (weighted mean difference= -0.031; 95% CI: -2.094 to 2.033; p=0.977). 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=0.107). The following limitations to the meta-analysis were reported: (1) only five 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 nonsteroidal anti-inflammatory drugs (NSAIDs) for knee osteoarthritis.[22,] Six studies were included (n=831 patients), with a range of follow-up from 5 to 26 weeks. Hyaluron injections were associated with statistically significant improvements in knee pain (standardized mean difference, 0.15; P =0.04) and function (standardized mean difference, 0.23; P = 0.01) 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 events 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.

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 control 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.[23,] 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>0.05). 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=0.018).

A RCT comparing intra-articular hyaluronan with corticosteroid injection in patients who had knee osteoarthritis was published by Askari et al (2016).[24] 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=0.720). 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=0.018).

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).[25] 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=0.0007), respectively.

Hermans et al (2019) conducted an open label RCT in individuals aged 18-65 years with symptomatic knee osteoarthritis (Kellgren and Lawrence I-III).[26] 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 ≥ 50% improvement from baseline and ≥20 mm absolute improvement from baseline on WOMAC visual analog scale pain subscore. The response rate based on pain during activity was 54.5% vs 34.2% (p=0.015). The intervention group showed a statistically significant improvement based on individual response domains for pain during rest (p=0.010), knee-related function (p=0.010), and patient's global assessment (p<0.0001). 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).[27] A total of 331 patients (90%) completed the study through 6 months of follow-up. The primary effectiveness endpoint was defined as ≥ 50% improvement from baseline and ≥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 vs saline group at 2 weeks (44.38 vs 34.12; p<0.001), 4 weeks (49.11 vs 45.29; p=0.003), and 6 months (51.14 vs 48.97; p=0.043). No clinically significant differences between groups were observed in the hyaluronic acid vs saline group at 8 weeks (55.03 vs 50.00; p=0.090), 12 weeks (52.53 vs 52.63; p=0.333), and 20 weeks (54.27 vs 55.36; p=0.835). 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 two 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 patients with osteoarthritis of joints other than the knee.

The question addressed in this evidence review is: Does intra-articular injection of hyaluronan improve the net health outcome in patients with osteoarthritis of the knee and other joints (e.g., hip, shoulder)?

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

Patients
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.

Patients with osteoarthritis of joints other than the knee are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

Comparators
Comparators of interest include physical therapy, medication, and surgery. Medications used for treatment include nonsteroidal anti-inflammatory drugs, 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. All of the comparators of interest are managed by physical therapists, orthopedic surgeons, and primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, and treatment-related morbidity.

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 intra-articular hyaluronan injections as a treatment for osteoarthritis of joints other than the knee has varying lengths of follow-up, ranging from three months to two years. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, two 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
Evidence was examined from published RCTs and systematic reviews.

Ankle Osteoarthritis
Vannabouathong et al (2018) published a systematic review of intra-articular injections for the treatment of ankle osteoarthritis.[28] 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=0.03). Study heterogeneity was low (I2 = 0%; p=0.41).

A Cochrane review by Witteveen et al (2015) addressed intra-articular hyaluronan and other conservative treatments for ankle osteoarthritis.[29] Reviewers identified six 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 one 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 two of the three 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 six 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.[30] They identified 3 small RCTs with a total of 75 patients, and 4 case series. In two 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

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.[31] 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

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.[32] 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.[33] Six trials (total n=428 patients) were included in the meta-analyses; 169 patients were treated with hyaluronan acid, 147 with corticosteroids, and 74 with placebo. In 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.[34] Meta-analysis of two 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.[35] 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

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.[36] 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.[37] 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 two 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; $p<0.05$). The standardized mean difference for improvement in Lequesne Index scores and the WOMAC scores were -0.24 (95% CI, -0.50 to 0.02; $p>0.05$) and -0.13 (95% CI, -0.64 to 0.37;$p>0.05$), 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 (2019) published a systematic review and meta-analysis evaluating various intra-articular injections for hip osteoarthritis, including platelet-rich plasma, hyaluronic acid, corticosteroid, and hyaluronic acid with platelet-rich plasma.[38] A literature through April 2018 was performed identifying 11 RCTs representing 1,060 patients. Mean follow-up duration ranged from 3-12 months. Studies varied with regard to imaging method used for guidance (ultrasound

versus fluoroscopy). A pair-wise meta-analysis indicated that corticosteroid and hyaluronic acid were superior to control in reducing visual analog scale score at 1 and 3 months ($p<0.05$) and that corticosteroid was superior to hyaluronic acid in reducing visual analog scale score at 1 month ($p<0.05$). The authors recommends 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.[39] Although (several) trials demonstrated a significant decrease in visual analog scale pain scores from baseline, meta-analysis did not indicate VS was superior to placebo at follow-up time windows of 7-14 days, 28-30 days, or final visit.

Review characteristics and results are summarized in Table 3 and 4.

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

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Lieberman (2015)[36]	2002-2011	23	Patients with hip OA	3868 (12-2343)	RCT, Retrospective, Prospective	NR
Wu (2017)[37]	2005-2010	6	Patients with hip OA	NR	RCT	NR
Zhao (2019)[38]	2004-2017	11	Patients with hip OA	1060 (43-305)	RCT	3-12 mo
Liao (2019)[39]	2006-2018	5	Patients with hip OA	591 (42-357)	RCT	3-6 mo

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

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

Study	Decrease in VAS	Difference in Pooled Lequesne Index (SMD)	Difference in WOMAC Scores (SMD)
Lieberman (2015)[36]	-1.97[a]		
95% CI	2.93 to -1.12		
P-value	<0.001		
Wu (2017)[37]	-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	<0.05	<0.05	<0.05
Zhao (2019)[38]	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: 0.039, I^2=0% CS: 0.043, I^2=79.4%		0.770, I^2=98.6%

Study	Decrease in VAS	Difference in Pooled Lequesne Index (SMD)	Difference in WOMAC Scores (SMD)
Liao (2019)[39]	-0.14[b]		-0.28[b,d]
95% CI	-0.46 to 0.18		-0.60 to 0.05
P-value	0.38; I^2=63%		0.10; I^2=63%

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.

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.[40] 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 vs 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 found reductions in pain and functional outcomes at 3 and 6 months with intra-articular hyaluronan treatment.[41] 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) and with 5 weekly injections of saline.[42] 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 but 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 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.[43] 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.

RCT 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)[42]	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 two weekly injections of phosphate-buffered saline solution (n=218)	Five weekly 2-mL injections of phosphate-buffered saline solution (n=221)
Kwon (2013)[43]	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)	

RCT: randomized controlled trial; OA: osteoarthritis; NR: not reported; 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)[42]				
5-Injection	26.4±1.8			
3-Injection	26.3±1.8			
Control	23.0±1.8			
Kwon (2013)[43]				
HA		19.88mm	56.7%	7.3%
Control		16.29mm	66.0%	3.3%
P-value			0.1231	0.1977

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

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Blaine (2008)[42,]		3. Investigators had different levels of experience with the injections			
Kwon (2013)[43,]		3. Ultrasound or fluoroscopic guidance for injection was only used at the discretion of the investigators			

The study-level limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements;
5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

Study	**Allocation[a]**	**Blinding[b]**	**Selective Reporting[c]**	**Follow-Up[d]**	**Power[e]**	**Statistical[f]**
Blaine (2008)[42,]	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)[43,]	1. Randomization process not described					3. P-values and confidence intervals not reported for all results

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Follow-Up 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).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

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.

Summary of Evidence

For individuals who have osteoarthritis of the knee who receive intra-articular hyaluronan injections, the evidence includes randomized controlled trials (RCTs) and systematic reviews of RCTs. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. Many RCTs have been published over the last two decades. While outcomes of these RCTs have been mixed, the RCT evidence base is characterized by studies showing small treatment effects of intra-articular hyaluronan injections. 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 meta-analysis (2016) found more than a 3-fold larger treatment effect in small 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 treatment benefit that is clinically meaningful. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who have osteoarthritis of joints other than the knee who receive intra-articular hyaluronan injections, the evidence includes RCTs, systematic reviews of RCTs, and observational studies. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. 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 hip osteoarthritis). The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

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.

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 six months for repeat injections. In response to a question about total number of treatment courses, there was no consensus.

Practice Guidelines and Position Statements

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 2013, the guidelines from the American Academy of Orthopaedic Surgeons (AAOS) on treatment of osteoarthritis of the knee indicated that AAOS could not recommend using intra-articular hyaluronan for patients with symptomatic knee osteoarthritis.[7] This recommendation was strong, meaning that the quality of the supporting evidence was high. It was based on a meta-analysis of 3 high-strength and 11 moderate-strength 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. The AAOS indicated that practitioners should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present. These guidelines replaced 2008 guidelines, which included a statement that a recommendation could not be made for intra-articular hyaluronan due to inconclusive evidence.

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.[44] This was based on strong evidence as assessed in eight 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."[45] 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).[46] At 1, 3, and 6 months, clinically significant improvements were seen in pain, function, and quality of life measures.

American College of Rheumatology
In 2019, the American College of Rheumatology updated its guidelines on osteoarthritis of the hand, hip, and knee.[47] 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 zero 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 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 multi-joint osteoarthritis.[48]

National Institute for Health and Care Excellence
In 2014, the clinical guideline issued by the National Institute for Health and Care Excellence for osteoarthritis care and management stated: "Do not offer intra-articular hyaluronan injections for the management of osteoarthritis."[49]

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

Ongoing and Unpublished Clinical Trials
Some currently 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			
NCT03281837[a]	A Post-market, Single Blind, Multicenter, Randomized, Controlled Trial of HYMOVIS® Intra-articular Injections in Active Subjects With Knee Osteoarthritis	147	Jun 2020 (ongoing)
NCT02776514	Intraarticular Injections of Steroids, Hyaluronic Acid or Platelet Rich Plasma Versus Placebo for the Knee Osteoarthritis	240	Nov 2020 (recruiting)

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT02280538	Trial to Assess the Structural Effect and Long-term Symptomatic Relief of Intra-articular Injections of Hyaluronic Acid in Primary Knee OA (ViscOA)	300	Jan 2018 (unknown)
NCT03200288[a]	A Phase 3, Randomized, Double-blind ,Placebo-controlled Study to Evaluate the Clinical Performance and Safety of an Intra-articular Solution of High and Low Molecular Weight Hyaluronic Acid (HL-01) in the Treatment of Symptomatic Knee Osteoarthritis	720	Oct 2018 (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. 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.

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, GELSYN-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
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: "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: ▪ 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.

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