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Viscosupplementation for Osteoarthritis

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and this policy is not to be used for current claims adjudication or business purposes.

Viscosupplementation by intra-articular (IA) injections (a single, one-time dose, injection **OR** multiple injections done weekly) using a U.S. Food and Drug Administration (FDA)-approved hyaluronan preparation **may be considered medically necessary** for patients who meet **ALL** of the following **DOCUMENTED** criteria:

1. Symptomatic, painful osteoarthritis (OA) of the knee interfering with functional activities (such as walking and/or standing) for a minimum of six months AND at least 5 of the following:
   - Bony enlargement,
   - Bony tenderness,
   - No palpable warmth,
   - Age >50 years,
   - Morning stiffness lasting <30 minutes,
   - Crepitus on knee motion,
   - Erythrocyte sedimentation rate <40 mm/hr,
   - Rheumatoid factor <1:40,
   - Synovial fluid signs of OA (clear, viscous, or white blood cell count <2,000/mm^3); **AND**
2. Osteophytes of the knee **OR** OA of the knee, confirmed by imaging; **AND**
3. Cause of pain cannot be attributed to other forms of joint disease; **AND**
4. Failure to respond to a comprehensive treatment program for six months and meet **any three** of the following **DOCUMENTED** criteria:
   - Conservative therapy, which includes use of pharmacologic therapy (such as acetaminophen, a non-steroidal anti-inflammatory drug [NSAID] up to four times daily, topical anti-inflammatory preparations containing capsaicin cream applied to affected knee joint) for minimum of three months without functional relief, **OR**
   - Physical therapy to the affected knee joint; **OR**
   - Participation in an exercise program; **OR**
   - Utilization of an orthotic device (such as a knee brace) applied to the affected knee joint; **OR**
   - Aspiration of the affected knee joint; **OR**
   - Injection(s) of IA steroids to the same affected knee joint; **OR**
   - The patient is unable to utilize conservative therapy due to adverse effects.

Repeat treatment cycle using an FDA-approved hyaluronan preparation **may be considered medically necessary** for patients who meet **ALL** of the following **DOCUMENTED** criteria:

1. Six months or more have elapsed since the initial or prior treatment cycle; **AND**
2. Significant improvement in pain and functional capacity as a result of previous treatment cycles (e.g., reduction in use of pain relievers like NSAIDs or opioids).

Viscosupplementation by IA injections using hyaluronan for the treatment of diseases of the knee that are not related to OA, including but not limited to chondromalacia patellae or osteochondritis dissecans, **are considered experimental, investigational, and/or unproven.**

Viscosupplementation by IA injections using hyaluronan for the treatment of OTHER joints (such as the foot, ankle, hip, spine, thumb, wrist, elbow, shoulder, and temporomandibular joint) **are considered experimental, investigational, and/or unproven**.

Policy Guidelines

None.

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), the U.S. Food and Drug Administration (FDA) approved indication. Other joints (e.g., hip, shoulder) are being investigated for IA hyaluronan treatment of OA.

Knee Osteoarthritis

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

A diagnosis of knee OA may be determined by utilizing the following Clinical Classification Criteria from the American College of Rheumatology (ACR). (1)

Table 1. Clinical Classification Criteria

Clinical and Laboratory	Clinical and Radiographic	Clinical
Positive knee pain with at least 5 of 9 symptoms below: • Age >50 • Stiffness <30 minutes • Crepitus • Bony tenderness • Bony enlargement	Positive knee pain with at least 1 of 3 symptoms below: • Age >50 • Stiffness <30 minutes • Crepitus + osteophytes	Positive knee pain with at least 3 or 4 of 6 symptoms below: • Age >50 • Stiffness <30 minutes • Crepitus • Bony tenderness

• No palpable warmth • Erythrocyte sedimentation rate (Westergren) (ESR) <40 mm/hour • Rheumatoid factor (RF) <1:40 • Synovial fluid signs of OA (clear, viscous, or white blood cell count <2,000/mm^3).		• Bony enlargement • No palpable warmth
92% sensitive 75% specific	91% sensitive 86% specific	3 of 6: 95% sensitive 69% specific 4 of 6: 84% sensitive 89% specific

Treatment

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

IA injection of hyaluronan has been proposed as a means of restoring the normal viscoelasticity of the synovial fluid in individuals with OA 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 OA, the overall length of hyaluronan chains present in cartilage and the hyaluronan concentration in the synovial fluid are decreased.

Regulatory Status

Several preparations of IA hyaluronan have been approved by the FDA as an alternative to nonsteroidal anti-inflammatory drug therapy in the treatment of OA of the knee, including but not limited to: 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™ (ZimmerBiomet); and Triluron™ (Fidia Farmaceutici). Most products are manufactured from rooster combs, except for Durolane®, Euflexxa®, Orthovisc®, Monovisc®, GELSYN™, Hymovis, TriVisc 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®, IA hyaluronan is "indicated for the treatment of pain in OA 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 IA 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 OA 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 OA 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. 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.

The FDA has not approved IA hyaluronan for joints other than the knee.

FDA product code: MOZ.

Treatment Series or Cycles

Treatment with IA injections of hyaluronan is proven for pain due to OA of the knee when administered according to the FDA labeled indications. (2)

Table 2. Intra-Articular Injection Cycles for Hyaluronan Preparations

Product	Number of injections per treatment cycle (per knee)
Euflexxa® (Nuflexxa, Viscosup)	3 injections per knee
Visco-3™	3 injections per knee
Hyalgan® (Hyaluronan, Hylan G-F20, Hylan Gel-Fluid)	3-5 injections per knee
Orthovisc®	3-4 injections per knee
Supartz®	3-5 injections per knee
Synvisc®	3 injections per knee

Synvisc-One™	1 injection per knee
Gel-One®	1 injection per knee
MONOVISC™	1 injection per knee
Gel-Syn™	3 injections per knee
HYMOVIS®	2 injections per knee
GenVisc® 850	3-5 injections per knee
Durolane®	1 injection per knee
Trivisc™	3 injections per knee
Synojoynt™	3 injections per knee
Triluron™	3 injections per knee

Rationale

This medical policy was created in May 1998 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through February 26, 2024.

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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 (IA) 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 (OA) of the knee.

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

Populations
The relevant population of interest is individuals with OA of the knee.

Interventions
The therapy being considered is IA hyaluronan injections.

IA injection of hyaluronan into OA 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, and surgery and intra-articular corticosteroids. Medications used for treatment include nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, dietary supplements, and narcotics. Surgeries for OA 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 3).

Table 3. 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 IA hyaluronan injections as a treatment for OA 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:

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

Systematic Reviews

A number of additional systematic reviews and meta-analyses have been published. (4-13) Some of these systematic reviews reported pooled analyses synthesizing results of RCTs that compared IA hyaluronan with placebo, and reported the outcome, pain. (4-6, 8, 13) Three of the new meta-analyses concluded that IA hyaluronan injections for knee OA provided a clinically meaningful reduction in pain compared with placebo. (5, 6, 8) One meta-analysis (Jevsevar et al. [2015] [4]) concluded that evidence from trials at low-risk of bias (e.g., double-blind, sham-controlled) did not demonstrate a clinically meaningful benefit of IA hyaluronan. Two of the meta-analyses concluding benefit of IA 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. (3, 12)

The O'Hanlon (2016) meta-analysis of placebo-controlled, blinded trials found a standardized mean difference of -0.23. (12) In contrast, the Johansen (2016) meta-analysis of placebo-controlled trials found a standardized mean difference of -0.39. (3) 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. (3) 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 IA hyaluronan literature. (14) 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 IA 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. (12)

Ran et al. (2018) published a meta-analysis of studies comparing IA hyaluronic acid and IA methylprednisolone as treatments for knee OA. (15) 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).

Miller et al. (2020) conducted a systematic review and meta-analysis of RCTs of IA hyaluronan treatment compared to NSAIDs for knee OA. (16) Six studies were included (N=831 patients),

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=0.04) and function (standardized mean difference [SMD], 0.23; p=0.01) compared with NSAIDs. The risk of overall adverse events was lower with IA 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.

Phillips et al. (2020) published a systematic review and network meta-analysis comparing IA high molecular weight hyaluronic acid, low molecular weight hyaluronic acid, standard-release corticosteroids, extended-release corticosteroids, platelet-rich plasma, and saline for knee OA. (17) 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.

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 OA. (18) Patients received 1 injection of IA 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 IA hyaluronan group and 21 in the corticosteroid group (p>0.05).

A RCT comparing IA hyaluronan with corticosteroid injection in patients who had knee OA was published by Askari et al. (2016). (19) Like the Tammachote (2016) study, it 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 VAS score at 3 months was 6.70 in the IA hyaluronan group and 6.26 in the corticosteroid group (p=0.720).

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). (20) 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 OA (Kellgren and Lawrence I-III). (21) 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 VAS 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).

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 OA compared to saline injection (n=185; intent-to-treat=184). (22) 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 VAS 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<0.001), 4 weeks (49.11 vs 45.29; p=0.003), and 6 months (51.14 vs 48.97; p=0.043).

Section Summary: Knee OA

In regard to the treatment of knee OA, 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 IA hyaluronan treatment. 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.

Osteoarthritis of Joints Other Than the Knee

Clinical Context and Therapy Purpose

The purpose of IA 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 OA of joints other than the knee.

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

Populations

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

Interventions
The therapy being considered is IA hyaluronan injections.

IA injection of hyaluronan into OA 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, and surgery and intra-articular corticosteroids. Medications used for treatment include NSAIDs, analgesics, dietary supplements, and narcotics. Surgeries for OA 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 4).

Table 4. Outcomes of Interest for Individuals with OA 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 IA hyaluronan injections as a treatment for OA 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:

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

Ankle Osteoarthritis
Systematic Reviews
Vannabouathong et al. (2018) published a systematic review of IA injections for the treatment of ankle OA. (23) 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 OA 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 (I^2 = 0%; p=0.41).

A Cochrane review by Witteveen et al. (2015) addressed IA hyaluronan and other conservative treatments for ankle OA. (24) Reviewers identified six RCTs, three of which were double-blind and compared IA hyaluronan with placebo. The other trials were single-blind. Two of them compared IA 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 six 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 IA hyaluronan with placebo. Meta-analyses of efficacy outcomes (pain, function) did not find a statistically significant benefit favoring IA 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 IA 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 IA hyaluronan for ankle OA, considered RCTs and observational studies. (25) They identified 3 small RCTs with a total of 75 patients, and 4 case series. In two of the RCTs, IA hyaluronan was compared with placebo injection and the third RCT compared IA 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 IA hyaluronan injections in the foot. Munteanu et al. (2011) reported on an RCT of a single IA hyaluronan injection in 151 patients with first metatarsophalangeal joint OA. (26) At the 1-, 3-, and 6-month follow-ups, there were no significant differences between the IA hyaluronan and placebo groups on the Foot Health Status Questionnaire.

Thumb or Hand Osteoarthritis

Systematic Reviews

Three systematic reviews have evaluated IA hyaluronan and corticosteroid injections for treating thumb OA. Kroon et al. (2016) identified 3 studies comparing IA hyaluronan with placebo and 6 comparing IA hyaluronan and corticosteroids. (27) Findings from the IA hyaluronan studies were not pooled.

A systematic review by Trellu et al. (2015) included only RCTs and pooled study data. (28) 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 IA hyaluronan with placebo (74 patients in each arm), there was no significant between-group difference in pain at week 12 (standardized response mean [SRM], -0.95; 95% CI, -3.87 to 1.97); however, functional capacity at week 12 was significantly better after IA hyaluronan than after placebo (SRM = -1.14; 95% CI, -1.69 to -0.60). When IA 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 IA hyaluronan and corticosteroids in functional capacity, IA hyaluronan was superior on pulp pinch force status (SRM = -1.66; 95% CI, -0.75 to -2.57), and corticosteroids were superior on pain (SRM=1.44; 95% CI, 0.14 to 2.74).

Riley et al. (2019) conducted a systematic review of injection therapies for base of thumb OA. (29) Meta-analysis of 2 RCTs that compared corticosteroid injections to IA hyaluronan (92 patients) demonstrated reduced visual analogue scale pain on activity with corticosteroid versus IA 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 OA with a systematic literature review through 2017. (30) No clear beneficial effect was shown for IA thumb base injections of hyaluronic acid. This evidence review informed the 2018 update of the European League Against Rheumatism management recommendations for hand OA.

Hip Osteoarthritis

Systematic Reviews

A systematic review by Lieberman et al. (2015) included RCTs and observational studies (with a minimum of 10 patients) evaluating IA hyaluronan for treatment of pain associated with hip OA. (31) Twenty-three studies were identified, six of which were RCTs. The studies evaluated 11 different formulations of IA 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 VAS. Reviewers did not report the number of points on the VAS but presumably this differed across studies and reviewers appeared to standardize results on a 10-point VAS. 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 VAS (95% CI, -2.83 to -1.12). In a pooled analysis of the 6 RCTs, there was a significantly greater decrease in pain with IA hyaluronan than with a control intervention (-0.27 points on a VAS; 95% CI, -0.43 to -0.11). Although statistically significant, a between-group difference of 0.27 points on a VAS 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 OA. (32) Six studies were selected. To measure the effects of hyaluronan injection, a series of pain and functionality assessments were conducted

using a VAS, the Lequesne Index, and the WOMAC. All six 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 SMD 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. (2020) published a systematic review and meta-analysis evaluating various IA injections for hip OA, including platelet-rich plasma, hyaluronic acid, corticosteroids, and hyaluronic acid with platelet-rich plasma. (33) A literature review through April 2018 was performed identifying 11 RCTs, representing 1,060 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 VAS score at 1 and 3 months ($p<0.05$) and that a corticosteroid injection was superior to hyaluronic acid in reducing VAS score at 1 month ($p<0.05$). The authors recommend corticosteroid injections as the most efficient agent for hip OA 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 OA treated with IA viscosupplementation. (34) Although several trials demonstrated a significant decrease in VAS 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 IA corticosteroid, hyaluronic acid, and platelet-rich plasma injections for the treatment of hip OA. (35) 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 IA 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 Table 5 and 6.

Table 5. Hip Osteoarthritis Systematic Reviews and Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Lieberman et al. (2015) (31)	2002-2011	23	Patients with hip OA	3868 (12-2343)	RCT, Retrospective, Prospective	NR

Wu et al. (2017) (32)	2005-2010	6	Patients with hip OA	NR	RCT	NR
Zhao et al. (2019) (33)	2004-2017	11	Patients with hip OA	1060 (43-305)	RCT	3-12 mo
Liao et al. (2019) (34)	2006-2018	5	Patients with hip OA	591 (42-357)	RCT	3-6 mo
Gazendam et al. (2020) (35)	Through 2019	11	Patients with hip OA	1353 (43-357)	RCT	2-6 mo

OA: osteoarthritis; mo: month(s); NR: not reported; RCT: randomized controlled trial.

Table 6. Hip Osteoarthritis Systematic Reviews and Meta-Analysis Results

Study	Decrease in VAS	Difference in Pooled Lequesne Index (SMD)	Difference in WOMAC Scores (SMD)
Lieberman et al. (2015) (31)	-1.97[a]		
95% CI	2.93 to -1.12		
P-value	<0.001		
Wu et al. (2017) (32)	-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 et al. (2019) (33)	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%
Liao et al. (2019) (34)	-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%
Gazendam et al. (2020) (35)	-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 IA hyaluronan for treatment of glenohumeral OA in adults. (36) Eight studies met the eligibility criteria; two were RCTs, five were prospective case series, and one 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 IA hyaluronan vs placebo or an alternative intervention for treating shoulder OA.

Zhang et al. (2019) published a systematic review and meta-analysis of studies of IA hyaluronan for treatment of glenohumeral OA that found reductions in pain and functional outcomes at 3 and 6 months with IA hyaluronan treatment. (46) 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 OA, 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. (38) Approximately 60% of patients had OA, although most with OA 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 VAS) in reported pain in both treatment groups at 26 weeks compared with placebo among patients with OA. In those without OA, there were no significant improvements with either regimen. Of note, this appears to be an as-treated analysis of the OA 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 IA hyaluronan in 300 patients with glenohumeral OA. (39) Intention-to-treat analysis found similar improvements from baseline in 100-mm VAS for pain (19.88 mm for IA 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 IA hyaluronan, 34.9% for sham) at 26 weeks. In a subset of IA hyaluronan patients, there were statistically significant differences of 4.0 mm in VAS 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 7 and 8. Study relevance, design, and conduct limitations are summarized in Table 9 and 10.

Table 7. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions		
					Active	**Comparator (1)**	**Comparator (2)**
Blaine et al. (2008) (38)	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 et al. (2013) (39)	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)	

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

Table 8. 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 et al. (2008) (38)				
5-Injection	26.4±1.8			
3-Injection	26.3±1.8			
Control	23.0±1.8			
Kwon et al. (2013) (39)				
HA		19.88 mm	56.7%	7.3%

Control		16.29 mm	66.0%	3.3%
P-value			0.1231	0.1977

AE: adverse event; HA: sodium hyaluronate; RCT: randomized controlled trial; VAS: visual analog score; Wk: week(s).

Table 9. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Blaine et al. (2008) (38)		3. Investigators had different levels of experience with the injections			
Kwon et al. (2013) (39)		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 literature review; this is not a comprehensive gaps 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 10. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow-Up[d]	Power[e]	Statistical[f]
Blaine et al. (2008) (38)	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 et al. (2013) (39)	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 literature 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.

[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: OA in Joints Other Than the Knee

The evidence for use of IA 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 VAS for studies on hip OA). There were fewer published studies on treating foot joints and spine OA.

Summary of Evidence

For individuals who have osteoarthritis (OA) of the knee who receive intra-articular (IA) 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 IA hyaluronan injections. 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 that there is a clinically

significant benefit. The evidence is sufficient to determine that the technology is likely to improve the net health outcome.

For individuals who have OA of joints other than the knee who receive IA 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 OA). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 IA hyaluronan for "appropriate" patients with knee OA based on high-quality evidence. (6) Patient selection criteria included individuals age 60 and older with Kellgren-Lawrence grade 2 or 3 OA. The Society also "suggests" IA hyaluronan for patients under age 60 with knee OA based on moderate-quality indirect evidence.

American Academy of Orthopedic Surgeon (AAOS)

In 2021, the guidelines from the American Academy of Orthopaedic Surgeons (AAOS) on treatment of OA of the knee indicated that AAOS does not recommend routine use of IA hyaluronic acid for patients with symptomatic knee OA. (40) 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.

In 2017, the AAOS clinical practice guidelines on hip OA included a recommendation that IA hyaluronic acid could not be recommended in patients with symptomatic hip OA, because it was not better than a placebo. (41) This was based on strong evidence as assessed in eight high-quality studies that evaluated IA hyaluronan against corticosteroids and placebo. Several studies showed no difference in patient pain and function after treatment with IA hyaluronan against placebo. Studies reviewing different formulations of IA hyaluronan were also considered.

In 2009 (reaffirmed 2014), the AAOS clinical practice guidelines on glenohumeral joint OA included a weak grade C recommendation that "The use of injectable viscosupplementation is an option when treating patients with glenohumeral [shoulder] osteoarthritis." (42) 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 OA of the glenohumeral joint who received 3, weekly IA injections of hylan G-F 20 (Synvisc). (43) At one, three, and six 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." (44)

American College of Rheumatology (ACR)

In 2019, the American College of Rheumatology updated its guidelines on OA of the hand, hip, and knee. (45) A conditional recommendation against the use of IA hyaluronic acid was given for the treatment of OA of the knee and first carpometacarpal joint of the hand. The College also made a strong recommendation against the use of IA hyaluronic acid for the treatment of OA 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 OA 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 (OARSI)

In 2014, the OARSI guidelines, developed by consensus after review of existing guidelines and systematic reviews, gave an “uncertain” recommendation for the use of IA hyaluronan for knee OA and a recommendation of “not appropriate” for multijoint OA. (46)

In 2019, OARSI updated these guidelines, as derived from expert consensus and review of high-quality meta-analytic data. IA hyaluronic acid was conditionally recommended for the treatment of knee OA 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 OA was not recommended. (47)

National Institute for Health and Clinical Excellence (NICE)

In 2022, the clinical guideline issued by the NICE for OA diagnosis and management stated: “Do not offer intra-articular hyaluronan injections for the management of osteoarthritis.” (48)

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 11.

Table 11. Summary of Key Trials

NCT Number	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 co-sponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	20610, 20611
HCPCS Codes	J3490, J7318, J7320, J7321, J7322, J7323, J7324, J7325, J7326, J7327, J7328, J7329, J7331, J7332

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/31/2025	Document became inactive.
07/15/2024	Reviewed. No changes.
11/15/2023	Document updated with literature review. Coverage unchanged. References 13, 20, 40, and 48 added; others removed.
10/01/2023	Document updated with preferred drug language/criteria.

12/01/2021	Document updated with literature review. Coverage unchanged. Added/updated the following references: 2-4, 7, 8, 11-14, 17, 19-22, 27-29, 31-35, 41, 42, 45-47, 49, 55, 56 and 58.
10/15/2020	Reviewed. No changes.
11/15/2019	Document updated with literature review. Coverage unchanged. Added references: 3-4.
10/15/2019	Document updated with literature review. The following change was made to Coverage: Modified conditional medical necessity criteria language specific to symptomatic, painful osteoarthritis of the knee. Added references: 2, 5, 9-18, 20, and 27.
04/01/2018	Document updated with literature review. Coverage unchanged. Added references 53, 54.
07/15/2017	Reviewed. No changes
01/01/2017	Document updated with literature review. Coverage unchanged.
11/01/2015	Document reviewed. Removed from Repeat treatment cycle criteria "Reduction of NSAIDs usage for six months following the previous treatment cycle" and incorporated it into the following criteria "Significant improvement in pain and functional capacity as a result of previous treatment cycles (e.g. reduction in use of pain relievers like NSAID or opioids).
02/15/2014	Document updated with literature review. Removed "at rest" to the coverage criteria; Symptomatic, painful osteoarthritis (OA) of the knee at rest.
09/01/2010	Document updated with literature review. The following changes were made: (1) revision of medical necessity criteria for comprehensive treatment program for six months prior to injection treatment; and (2) viscosupplementation for osteochondritis dissecans of the knee or for osteoarthritis of other joints (such as foot, spine, thumb, wrist, elbow, and temporomandibular joint) are considered experimental, investigational, and/or unproven.
09/15/2009	Revised and updated entire document. Coverage remains conditional for the affected knee. FDA approved single injection treatment information added to policy. This policy is no longer scheduled for routine literature review and update.
09/15/2007	Revised/updated entire document
01/01/2007	New CPT/HCPCS code(s) added
08/15/2003	Revised/updated entire document
05/01/1998	New medical document