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 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
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Original Effective Date: July 1, 2007
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Current Effective Date: July 22, 2016

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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 policy is to determine whether intra-articular injection of hyaluronan improves the net health outcome in patients with osteoarthritis of the knee and other joints (eg, hip, shoulder).

BACKGROUND
Knee Osteoarthritis
Knee osteoarthritis (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.

Treatment
Currently, no curative therapy is available for OA, 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 OA and improving pain and 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 intra-articular (IA) 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 (OA) 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 the manufacturer’s prescribing information for Synvisc and Euflexxa, IA 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, eg, acetaminophen.” The product inserts further indicate that Synvisc and Euflexxa should be injected intra-articularly into the knee joint once per week for a total of 3 injections over a 2- to 3-week period. In contrast, 5 weekly injections are recommended for the Hyalgan and Supartz products, and 3 to 4 weekly injections are recommended for Orthovisc. In February 2009, FDA approved the use of single-dose hylan G-F 20 (Synvisc-One) for the treatment of OA of the knee. In 2011, 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 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, FDA approved removal of a precautionary statement from the package inserts for Hyalgan® and Synvisc® that stated that the safety and efficacy of repeat courses have 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 MEDLINE database. The most recent literature review was performed through February 18, 2019.

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 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 (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 the knee.

The question addressed in this evidence review is: does IA injection of hyaluronan improve the net health outcome in patients with OA of the knee and other joints (eg, hip, shoulder)?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals with OA of the knee.
**Interventions**
The therapy being considered is IA hyaluronan injections.

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.

**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 OA 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**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
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<tbody>
<tr>
<td>Symptoms</td>
<td>Pain, inflammation, limited range of motion, depression or anxiety</td>
</tr>
<tr>
<td>Functional outcomes</td>
<td>Increased range of motion, increased mobility, and reduction of pain</td>
</tr>
</tbody>
</table>

**Timing**
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 one outcome of interest, longer follow-up was necessary to fully observe outcomes.

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

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:
- a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- d. Studies with duplicative or overlapping populations were excluded.

This evidence review was informed by a TEC Assessment (1998) on IA hyaluronan injections for OA,\(^1\) 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 OA of the knee.\textsuperscript{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 IA hyaluronan because the technical expert panel concluded the evidence did not need updating.\textsuperscript{5}

The 2014 TEC Assessment involved a systematic review of recent meta-analyses on the treatment of knee OA with IA hyaluronan injections.\textsuperscript{3} Included in the evaluation were 5 meta-analyses published between 2011 and 2013.\textsuperscript{6,7,8,9,10} Two meta-analyses concluded that IA 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.\textsuperscript{7} It is also possible the results supporting a clinically meaningful benefit were biased in favor of IA 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 IA hyaluronan over placebo.

Literature reviews in 2016 and 2017 identified a number of additional systematic reviews and meta-analyses published after the 2014 TEC Assessment.\textsuperscript{11,12,13,14,15,16,17,18,19,20} Some of these systematic reviews reported pooled analyses synthesizing results of RCTs that compared IA hyaluronan with placebo, and reported the outcome, pain.\textsuperscript{12,13,14,16} Three of the new meta-analyses concluded that IA hyaluronan injections for knee OA provided a clinically meaningful reduction in pain compared with placebo.\textsuperscript{13,14,16} One meta-analysis (Jevsevar et al [2015])\textsuperscript{12} concluded that evidence from trials at low-risk of bias (eg, 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, and clinical significance depends on the threshold used.\textsuperscript{11,20} As noted in the 2014 TEC Assessment, "...for a standardized mean difference (SMD), a minimally important difference of -0.37 is sometimes cited...." The O’Hanlon (2016) meta-analysis of placebo-controlled, blinded trials found an SMD of -0.23.\textsuperscript{20} In contrast, the Johansen (2016) meta-analysis of placebo-controlled trials found an SMD of -0.39.\textsuperscript{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.\textsuperscript{11} Moreover, a stratified analysis by trial size found an SMD of -0.72, whereas trials with at least 100 patients showed an SMD 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.\textsuperscript{5} 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.\(^{20}\) 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 IA hyaluronan on health outcomes in patients with knee OA.

Ran et al (2018) published a meta-analysis of studies comparing IA hyaluronic acid and IA methylprednisolone as treatments for knee OA\(^ {21}\). 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.

While no placebo-controlled randomized trials published after the 2014 TEC Assessment were identified, 2 RCTs from 2016, did compare IA hyaluronan with corticosteroid injection. Neither found a clinically meaningful benefit of IA hyaluronan compared with corticosteroids. Limitations of both trials included lack of a placebo control group, making conclusions about the efficacy of IA 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.\(^ {22}\) 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 [VAS]), did not differ significantly between groups. Mean VAS score at 6 months was 24 in the IA 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 VAS score, 14) than in the IA hyaluronan group (mean VAS score, 23; \(p=0.018\)).

The other RCT comparing IA hyaluronan with corticosteroid injection in patients who had knee OA was published by Askari et al (2016).\(^ {23}\) 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 VAS. 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 (\(p=0.720\)). After 1 month, mean pain score was significantly lower in the corticosteroid group (mean VAS score, 5.59) than the IA hyaluronan group (mean VAS score, 6.63; \(p=0.018\)).

**Section Summary: Knee OA**

In regard to the treatment of knee OA, 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 IA 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 (ie,
＞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.

OA 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 question addressed in this evidence review is: does IA injection of hyaluronan improve the
net health outcome in patients with OA of the knee and other joints (eg, hip, shoulder)?

The following PICOTS were used to select literature to inform this review.

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

Interventions
The therapy being considered is IA hyaluronan injections.

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.

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 OA 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

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**Timing**
The existing literature evaluating IA intra-articular hyaluronan injections as a treatment for OA 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.

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

**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 OA**
Evidence was examined from published RCTs and systematic reviews. 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 (ie, 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.

**Foot OA**
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. 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 Osteoarthritis**
Two systematic reviews have evaluated IA hyaluronan and corticosteroid injections for treating thumb OA. The review by Kroon et al (2016) identified 3 studies comparing IA hyaluronan with placebo and 6 comparing IA hyaluronan and corticosteroids. Findings from the IA hyaluronan studies were not pooled. Unlike the Kroon et al (2016) review, the systematic review by Trellu et al (2015) included only RCTs and pooled study data. 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).

**Hip OA**
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. 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. 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.

**Table 3. Comparison of Trials/Studies Included in Systematic Reviews & Meta-Analysis for Hip OA**

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OA: osteoarthritis.

**Table 4. Hip OA Systematic Reviews & Meta-Analysis Characteristics**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
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<td>Lieberman (2015)</td>
<td>2002-2011</td>
<td>23</td>
<td>Patients with hip OA</td>
<td>3868 (12-2343)</td>
<td>RCT, Retrospective, Prospective</td>
<td>NR</td>
</tr>
<tr>
<td>Wu (2017)</td>
<td>2005-2010</td>
<td>6</td>
<td>Patients with hip OA</td>
<td>NR</td>
<td>RCT</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

**Table 5. Hip OA Systematic Reviews & Meta-Analysis Results**

<table>
<thead>
<tr>
<th>Study</th>
<th>Decrease in VAS</th>
<th>Difference in Pool Lequesne Index (SMD)</th>
<th>Difference in WOMAC Scores (SMD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lieberman (2015)</td>
<td>-1.97</td>
<td>2.93 to -1.12</td>
<td>-1.06 to -0.39</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td>-1.42 to -0.51</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Wu (2017)</td>
<td>-0.72</td>
<td>-0.74</td>
<td>-1.42 to -1.21</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td>-1.21</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

VAS: visual analog score; SMD: standard mean difference; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
CI: confidence interval.
Shoulder OA

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.31 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. The RCTs are described next.

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.32 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.33 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.

Table 6. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blaine (2008)32</td>
<td>US</td>
<td>79</td>
<td>NR</td>
<td>Patients with glenohumeral joint OA</td>
<td>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)</td>
</tr>
<tr>
<td>Kwon (2013)33</td>
<td>US</td>
<td>23</td>
<td>NR</td>
<td>Patients with glenohumeral OA</td>
<td>Three weekly injections of sodium hyaluronate (n=150) Three weekly injections of phosphate-buffered saline (n=150)</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; OA: osteoarthritis; NR: not reported.
Table 7. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean VAS Reduction from Baseline to 13 Wk.</th>
<th>Mean VAS Improvement from Baseline to 26 Wk.</th>
<th>Rate of Any AE</th>
<th>Rate of Serious AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blaine</td>
<td>26.4±1.8</td>
<td>26.3±1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kwon</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2013)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HA</td>
<td>19.88mm</td>
<td>56.7%</td>
<td>7.3%</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>16.29mm</td>
<td>66.0%</td>
<td>3.3%</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>0.1231</td>
<td>0.1977</td>
<td></td>
</tr>
</tbody>
</table>

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

Table 8. Relevance Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesd</th>
<th>Follow-Up e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blaine</td>
<td></td>
<td>3. Investigators had different levels of experience with the injections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kwon</td>
<td></td>
<td>3. Ultrasound or fluoroscopic guidance for injection was only used at the discretion of the investigators</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2013)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

a Population key: 1. Intended use population unclear; 2. 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 establish 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 9. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Follow-Up d</th>
<th>Power e</th>
<th>Statistical f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blaine</td>
<td></td>
<td></td>
<td>1. Randomization process not described</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2008)</td>
<td></td>
<td></td>
<td>1,2,3. Blinding not described</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Allocation concealment unclear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kwon</td>
<td>1. Randomization process not described</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2013)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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).

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
Intra-Articular Hyaluronan Injections for Osteoarthritis

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 (eg, 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 OA of the knee who receive IA hyaluronan injections, the evidence includes RCTs and systematic reviews of RCTs. The 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. 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 that 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 (ie, >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 OA of joints other than the knee who receive IA hyaluronan injections, the evidence includes RCTs, systematic reviews of RCTs, and observational studies. The 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 (eg, 0.27-point improvement on a 10-point visual analog scale for hip OA). The evidence is insufficient to determine the effects of the technology on health outcomes.

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 IA hyaluronan of the knee was medically necessary. In addition, those providing input supported an interval of 6 months for repeat injections. In response to a question about total number of treatment courses, there was no consensus.

**PRACTICE GUIDELINES AND POSITION STATEMENTS**

**American Medical Society for Sport Medicine**
The scientific statement from the American Medical Society for Sport Medicine (2016) recommended IA hyaluronan for “appropriate” patients with knee osteoarthritis (OA) based on high-quality evidence.\(^{14}\) 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 Orthopaedic Surgeons**
The guidelines from the AAOS (2013) on treatment of OA of the knee indicated that AAOS could not recommend using IA hyaluronan for patients with symptomatic knee OA.\(^{7}\) 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 IA hyaluronan due to inconclusive evidence.

The AAOS (2017) 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.\(^{34}\) 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. The AAOS (2009; reaffirmed 2014) 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.”\(^{35}\) 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).\(^{36}\) At one, three, and six months, clinically significant improvements were seen in pain, function, and quality of life measures.

**American College of Rheumatology**
The American College of Rheumatology (2012) updated its guidelines on OA of the hand, hip, and knee.\(^{37}\) A conditional recommendation was given for use of IA hyaluronan to treat OA of the knee. The College recommended not using IA hyaluronan for OA of the hand. For OA of the hip, the College explicitly made no recommendation due to the lack of randomized controlled trials. An update is anticipated in Spring 2019.
Osteoarthritis Research Society International
The Osteoarthritis Research Society International (2014) 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.38,

National Institute for Health and Care Excellence

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 10.

Table 10. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02776514</td>
<td>Steroids, Hyaluronic Acid or Platelet Rich Plasma Versus Placebo for the Knee Osteoarthritis (KIT)</td>
<td>240</td>
<td>July 2018</td>
</tr>
<tr>
<td>ENACT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>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</td>
<td>720</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT03281837</td>
<td>A Post-market, Single Blind, Multicenter, Randomized, Controlled Trial of HYMOVIS® Intra-articular Injections in Active Subjects With Knee Osteoarthritis</td>
<td>146</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02629380</td>
<td>Early Viscosupplementation After Partial Meniscectomy: a Double Blind, Placebo Controlled Randomized Trial</td>
<td>90</td>
<td>Mar 2016 (completed)</td>
</tr>
<tr>
<td>NCT02280538</td>
<td>Trial to Assess the Structural Effect and Long-term Symptomatic Relief of Intra-articular Injections of Hyaluronic Acid in Primary Knee OA (ViscOA)</td>
<td>300</td>
<td>Jan 2018 (unknown)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
<sup>a</sup> 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
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7318</td>
<td>Hyaluronan or derivative, durolane, for intra-articular injection, 1 mg</td>
</tr>
<tr>
<td>J7320</td>
<td>Hyaluronan or derivative, Genvisc 850, for intra-articular injection, 1 mg</td>
</tr>
<tr>
<td>J7321</td>
<td>Hyaluronan or derivative, Hylan G, Supartz or Visco-3, for intra-articular injection, per dose</td>
</tr>
</tbody>
</table>
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, GELESYN-3, for intra-articular injection, 0.1 mg
J7329  Hyaluronan or derivative, Trivisc, 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 Reference 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.

REFERENCES

Other References
2. Blue Cross and Blue Shield of Kansas Medical Advisory Committee, April 2007.
3. Blue Cross and Blue Shield of Kansas Family Practice Liaison Committee, July 2014.