Sodium Hyaluronate

Policy Number: 2023D0081H
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Instructions for Use

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Coverage Rationale

Gel-One, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz, Synojoynt, Synvisc or Synvisc-One, Triluron, TriVisc, and Visco-3 are typically excluded from coverage. Coverage reviews may be in place if required by law or the benefit plan. Refer to the Medical Benefit Drug Policy titled Medical Benefit Therapeutic Equivalent Medications – Excluded Drugs and the corresponding excluded drug list with preferred alternatives.

Note: For requests that require medical necessity review also refer to the Diagnosis-Specific Criteria section below (for Medicare reviews, refer to the CMS section**).

Coverage for Durolane, Euflexxa, and Gelsyn-3 is contingent on criteria in the Diagnosis-Specific Criteria section. Prior authorization is not required.

Diagnosis-Specific Criteria

Initial Authorization (Sodium Hyaluronate Naïve Patients)

Intra-articular injections of sodium hyaluronate are proven and medically necessary when all of the following are met:

- Diagnosis of knee osteoarthritis; **and**
- The member has not responded adequately to conservative therapy which may include physical therapy or pharmacotherapy (e.g., non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen and/or topical capsaicin cream) or injection of intra-articular steroids and such therapy has not resulted in functional improvement after at least 3 months, or the member is unable to tolerate conservative therapy because of adverse side effects; **and**
- The member reports pain which interferes with functional activities (e.g., ambulation, prolonged standing); **and**
- The pain is attributed to degenerative joint disease/primary osteoarthritis of the knee; **and**
- There are no contraindications to the injections (e.g., active joint infection, bleeding disorder); **and**
- Dosing is in accordance with the US FDA approved labeling as shown in the table below; **and**
- Initial authorization is for a single treatment course once per joint for 6 months (see table below).

Reauthorization/Continuation

Repeated courses of intra-articular hyaluronan injections may be considered when all of the following are met:

- Diagnosis of knee osteoarthritis; **and**
- Documentation of positive clinical response to therapy (e.g., significant pain relief was achieved with the prior course of injections); **and**
- Pain has recurred; **and**
- At least 6 months have passed since the prior course of treatment for the respective joint; **and**
- Dosing is in accordance with the US FDA approved labeling as shown in the table below; **and**
- Continuing authorization is for a single treatment course once per joint for 6 months (see table below).

The table below shows the FDA approved sodium hyaluronate products and their respective FDA labeled dosage per treatment course per joint:

FDA Labeling					
Durolane	1 injection	Hymovis	2 injections	Synvisc One	1 injection
Euflexxa	3 injections	Monovisc	1 injection	Triluron	3 injections
Gel One	1 injection	Orthovisc	3 to 4 injections	TriVisc	3 injections
Gelsyn-3	3 injections	Supartz	3 to 5 injections	Visco-3	3 injections
GenVisc 850	3 to 5 injections	Synojoynt	3 injections		
Hyalgan	5 injections	Synvisc	3 injections		

Intra-articular injections of sodium hyaluronate are unproven and not medically necessary for treating any other indication due to insufficient evidence of efficacy including, but not limited to the following:

- Hip osteoarthritis
- Temporomandibular joint osteoarthritis
- Temporomandibular joint disc displacement

Hyaluronic acid gel preparations to improve the skin's appearance, contour and/or reduce depressions due to acne, scars, injury or wrinkles are considered cosmetic and are not covered.

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

HCPCS Codes*	Required Clinical Information
Sodium Hyaluronate Product Therapy Using Preferred Products (Durolane, Euflexxa, and Gelsyn-3)	
J7318 J7323 J7328	Medical notes documenting **all** of the following: • Current prescription • Name and tax ID number of the servicing provider/facility to facilitate claim processing • Member diagnosis of OA of the knee • Conservative treatment tried for at least 3 months including response • Signs and symptoms • Current functional limitations • Complete report(s) of diagnostic imaging (X-ray, CT, or MRI reports) • Previous sodium hyaluronate treatment provided including the brand name of the drug, course of treatment, and response • Dose, frequency, interval since previous sodium hyaluronate treatment • Physician treatment plan

HCPCS Codes*	Required Clinical Information
Sodium Hyaluronate Product Therapy Using Non-Preferred Products (Gel-One, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz, Synojoynt, Synvisc or Synvisc-One, Triluron, TriVisc, Visco-3)	

J3490
J7320
J7321
J7322
J7324
J7325
J7326
J7327
J7329
J7331
J7332
	Initial Therapy
	Medical notes documenting **all** of the following:
	• Current prescription
	• Name and tax ID number of the servicing provider/facility to facilitate claim processing
	• Member diagnosis of OA of the knee
	• Conservative treatment of at least 3 months, including response
	• Signs and symptoms
	• Current functional limitations
	• Complete report(s) of diagnostic imaging (X-ray, CT, or MRI reports)
	• **One** of the following:
	  ○ **Both** of the following:
	  ▪ History of a trial of adequate dose and duration of Durolane, Gelsyn-3, and Euflexxa with minimal response; and
	  ▪ Attestation that the clinical response would be expected to be superior than experienced with Durolane, Euflexxa, and Gelsyn-3
	  or
	  ○ **Both** of the following:
	  ▪ History of intolerance, contraindication, or adverse event to Durolane, Euflexxa, and Gelsyn-3; and
	  ▪ Physician attests that, in their clinical opinion, the same intolerance, contraindication, or adverse event would not be expected to occur with Gel-One, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz, Synojoynt, Synvisc or Synvisc-One, Triluron, TriVisc, or Visco-3
	• Physician treatment plan
	
	Continuation of Therapy
	Medical notes documenting **all** of the following:
	• Reason for treatment, including positive response to previous treatments
	• Date duration of last treatment

*For code descriptions, refer to the Applicable Codes section.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
20605	Arthrocentesis, aspiration and/or injection, intermediate joint or bursa (e.g., temporomandibular, acromioclavicular, wrist, elbow or ankle, olecranon bursa); without ultrasound guidance
20606	Arthrocentesis, aspiration and/or injection, intermediate joint or bursa (e.g., temporomandibular, acromioclavicular, wrist, elbow or ankle, olecranon bursa); with ultrasound guidance, with permanent recording and reporting
20610	Arthrocentesis, aspiration and/or injection, major joint or bursa (e.g., shoulder, hip, knee, subacromial bursa); without ultrasound guidance
20611	Arthrocentesis, aspiration and/or injection, major joint or bursa (e.g., shoulder, hip, knee, subacromial bursa); with ultrasound guidance, with permanent recording and reporting

HCPCS Code	Description
J3490	Unclassified drugs
J7318	Hyaluronan or derivative, Durolane, for intra-articular injection, 1 mg
J7320	Hyaluronan or derivative, GenVisc 850, for intra-articular injection, 1 mg
J7321	Hyaluronan or derivative, Hyalgan, Supartz or Visco-3, for intra-articular injection, per dose
J7322	Hyaluronan or derivative, Hymovis, for intra-articular injection, 1 mg
J7323	Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose
J7324	Hyaluronan or derivative, Orthovisc, for intra-articular injection, per dose
J7325	Hyaluronan or derivative, Synvisc or Synvisc-One, for intra-articular injection, 1 mg
J7326	Hyaluronan or derivative, Gel-One, for intra-articular injection, per dose
J7327	Hyaluronan or derivative, Monovisc, for intra-articular injection, per dose
J7328	Hyaluronan or derivative, Gelsyn-3, for intra-articular injection, 0.1 mg
J7329	Hyaluronan or derivative, Trivisc, for intra-articular injection, 1 mg
J7331	Hyaluronan or derivative, Synojoynt, for intra-articular injection, 1 mg
J7332	Hyaluronan or derivative, Triluron, for intra-articular injection, 1 mg

Diagnosis Code	Description
M13.0	Polyarthritis, unspecified
M17.0	Bilateral primary osteoarthritis of knee
M17.10	Unilateral primary osteoarthritis, unspecified knee
M17.11	Unilateral primary osteoarthritis, right knee
M17.12	Unilateral primary osteoarthritis, left knee
M17.2	Bilateral post-traumatic osteoarthritis of knee
M17.30	Unilateral post-traumatic osteoarthritis, unspecified knee
M17.31	Unilateral post-traumatic osteoarthritis, right knee
M17.32	Unilateral post-traumatic osteoarthritis, left knee
M17.4	Other bilateral secondary osteoarthritis of knee
M17.5	Other unilateral secondary osteoarthritis of knee
M17.9	Osteoarthritis of knee, unspecified

Background

Sodium hyaluronate, also referred to as hyaluronic acid (HA) or hyaluronan, is a component of normal synovial fluid, which lubricates the joints and absorbs shock. Intra-articular (IA) injections of HA help replace or supplement that which is lost. Commercially prepared and ready for injection, HA products differ by molecular weight and cross-linkage, and may be derived from bacterial fermentation or extracted from avian products (Hayes, 2018).

HA preparations have been approved by the FDA as a device for the treatment of pain in knee OA in individuals who have not responded to exercise, physical therapy (PT) and nonprescription analgesics. HA gels have also been approved by the FDA for treatment of wrinkles and other facial contouring disorders. There is no evidence that use of one IA hyaluronon product is superior to another.

Numerous randomized controlled trials (RCTs) have investigated the utility of sodium hyaluronate for OA of the knee as well as for temporomandibular joint (TMJ) arthritis and disc displacement. There is growing literature regarding the use of Synvisc® Hylan G-F 20 for the treatment of OA of the hip. However, current FDA labeling for sodium hyaluronate is limited to OA of the knee.

Proven

Knee Osteoarthritis (OA)

A 2019 ECRI report on visco supplementation found evidence from 8 systematic reviews and 6 RCTs (total patients = 12,775) to be inconclusive for treating knee pain due to OA. While IA HA injections may provide relief in some patients, questions remain about the most effective formulations, which populations benefit most, and whether HA should be combined with other agents to increase efficacy.

Hayes conducted a comparative effectiveness review evaluating the efficacy and safety of IA injections with HA (IA-HA) versus injections with either saline (IA-S) or corticosteriods (IA-CS) for the treatment of knee OA. Systematic reviews assessed 971 to 4806 patients treated with IA-HA; additional RCTs each assessed 32 to 660 patients treated with IA-HA compared with IA-S, IA-CS, or other HA products. Follow up was usually 6 months. The moderate quality evidence suggested significantly better function with IA-HA than IA-S that may be clinically meaningful; however, no clinically significant incremental benefit in pain control was demonstrated. Evidence indicated significantly better pain control and functional outcomes after IA-HA versus IA-CS at 6 months, but did not consistently suggest clinical superiority at 6 months or differences at shorter durations of follow-up. Evidence suggests no substantive differences among products in terms of either safety or efficacy, and currently available evidence is inadequate to determine whether IA-HA leads to delays in knee replacement compared with the other studied treatment modalities or the different types of IA-HA. There were no concerns regarding to the safety of HA injections (2018).

Di Martino et al. (2018) conducted a blind, comparative RCT on individuals with degenerative knee disease, evaluating long-term clinical outcomes from IA injections of either platelet-rich plasma (PRP) or HA. Participants (N = 192) underwent 3 blinded weekly IA injections of either PRP or HA. Patients were prospectively evaluated pre-injection, and then at 2, 6, 12, and 24 months with a mean of 64.3 months of follow up. Primary outcomes were based on subjective IKDC evaluation, secondary outcomes based on EuroQol VAS and Tegner scores. The number of participants who reached the final evaluation was 167. Both treatments were effective in improving functional status and symptoms over time. Mean IKDC subjective score improved significantly for both groups and remained stable over time up to 24 months and at final evaluation. A comparative analysis showed no significant intergroup difference in any of the clinical scores at any follow-up point. The median duration of patient subjective perception of symptomatic relief was 9 months for HA and 12 months for PRP, which was considered insignificant. The only significant difference was observed in the rate of reintervention at 24 months, which was significantly lower in the PRP group (22.6% vs 37.1%). The researchers concluded that PRP did not provide an overall superior clinical improvement compared with HA in terms of either symptomatic-functional improvement at different follow-up points or effect duration (ClinicalTrials.gov identifier NCT01670578).

Ha and colleagues (2017) conducted a randomized, double-blind, multi-center, non-inferiority trial to assess the safety and efficacy of a cross-linked hyaluronate (XLHA, single injection form) compared with a linear high molecular hyaluronate (HMWHA, 3 injections) in patients with symptomatic knee OA. Two hundred eighty seven patients with grade I-III OA were randomized to each group. Three weekly injections were given in both groups, with 2 saline injections preceding XLHA injection to maintain double-blindness. Primary endpoint was the change of weight-bearing pain (WBP) at 12 weeks after the last injection. Secondary endpoints included the Western Ontario and McMaster Universities (WOMAC) OA Index; patient's and investigator's global assessment; pain at rest, at night, or in motion; proportion of patients achieving at least 40% decrease in WBP; and rate of rescue medicine use and its total consumption. Results demonstrated no significant difference between groups in all outcome measures. Injection site pain was the most common adverse event (AE) and no remarkable safety issue was identified. The authors concluded that a single injection of XLHA was non-inferior to three weekly injections of HMWHA in terms of WBP reduction, and supports XLHA as an effective and safe treatment for knee OA (ClinicalTrials.gov identifier NCT01510535).

A systematic review and meta-analysis by Bannuru et al. (2009) compared the effectiveness of IA HA (N = 312 patients) with corticosteroids (N = 294 patients) for knee OA. Of 1238 studies evaluated, 7 studies were included for meta-analysis. The authors found that IA corticosteroids appeared more effective for pain relief through week 4. At week 4, both treatments appeared equal. However, treatment effects at 8 weeks and beyond showed greater efficacy in the HA group.

Chevalier et al. (2010) conducted a prospective double-blind study of 253 patients to compare the use of a single 6 ml IA injection of hylan G-F 20 (N = 123) with placebo (N = 130) in patients with symptomatic knee OA. Outcomes were measured by

the WOMAC OA Index, Likert and patient global assessment (PGA) questionnaires as well as a blinded evaluator completed by the clinical observer global assessment (COGA). Patients were followed up at 1, 4, 8, 12, 18 and 26 weeks after injection. Patients receiving hylan G-F 20 had greater improvements in WOMAC A pain scores and several of the secondary outcome measures (WOMAC A1, PGA and COGA) than patients receiving placebo treatment. The authors concluded that a single 6 ml IA injection of hylan G-F 20 provided better pain relief over 26 weeks than placebo.

In a prospective, naturalistic study by Petrella (2005), 537 patients received a 3 IA injection series with Suplasyn (Synvisc in the United States) over 3 weeks. The cohort group was followed for 6.7 years. Patients returned for consideration of a repeat injection series based on their perception of symptom severity and were eligible if their resting visual analog scale (VAS) pain was > 45 mm. The 3-injection series and data collection were repeated and again, patients were given similar instructions regarding consideration of a third injection series. The mean time between first and second series was 27 +/- 7 wks. Duration of symptom control was about 6 months. These data support the potential role of IA HA as an effective long-term therapeutic option for patients with OA of the knee.

A systematic review and meta-analysis of 54 trials reported that HA is efficacious for treatment of knee pain by 4 weeks, reaches its peak of effectiveness at 8 weeks, and exerts a residual detectable effect at 24 weeks (Bannuru, 2011). However, other systematic reviews and a meta-analyses reported that evidence for clinical benefit is hindered by variable quality of trials, potential publication bias, and unclear clinical significance of some of the reported improvements (Rutjes, 2012; Samson, 2007).

A 40-month multicenter trial randomized 306 patients with knee OA to IA injection with placebo or 4 cycles of HA (each cycle consisted of one injection weekly for 5 weeks) and reported that repeated cycles of HA injection not only improved symptoms in between cycles compared with placebo, but also exerted a carryover effect for at least 1 year after the last cycle (Navarro-Sarabia, 2011). Similarly, an open-label extension study of 378 patients from a double-blind placebo RCT reported that a repeated series of 3 weekly IA injections of bioengineered hyaluronate given 23 weeks after the initial 3-injection treatment course was safe and effective for symptom relief (Altman et al., 2011).

Juni et al. conducted a comparative, multicenter, patient-blind, RCT in 660 patients with symptomatic knee OA. Patients were randomly assigned to receive 1 cycle of 3 IA injections per knee of 1 of 3 preparations: Orthovisc, Synvisc, or Ostenil. The primary outcome measure was the change in the WOMAC pain score at 6 months. Secondary outcome measures included local AEs (effusions or flares) in injected knees. During months 7-12, patients were offered a second cycle of viscosupplementation. The results showed similar pain relief in all 3 groups and no relevant differences in any of the secondary efficacy outcomes at 6 months. There was a trend toward more local AEs in the hylan group (Orthovisc) than in the other groups during the first cycle (difference 2.2%), and this trend became more pronounced during the second cycle (difference 6.4%). The authors concluded that there was no difference in efficacy between the 3 products (2007).

In a study included as part of the U.S. FDA premarket approval submission, Pavelka and Uebelhart (2011) performed a prospective, double-blind, multicenter, active control trial to assess clinical superiority between GelSyn (Sinovial) and Synvisc. A total of 380 patients with mild-to-moderate knee OA (mean age 65 years, mean duration of knee OA 7.6 years) who were given weekly IA injections of either GelSyn (N = 192) or Synvisc commercial hyaluronan (N = 188) for 3 consecutive weeks. The observation period was 6 months. Improvement was measured using the WOMAC pain subscore from baseline to the final visit (week 26). At week 26, WOMAC pain subscores decreased by a mean of 32.5 for both groups. Both preparations were well-tolerated, with no statistically significant differences in tolerability profile between groups. The conclusion was that both Sinovial and Synvisc were equally effective.

Newberry et al. conducted a systematic review under contract by the Agency for Healthcare Research and Quality (AHRQ), evaluating the effectiveness of HA in the treatment of severe degenerative joint disease (DJD) of the knee. The authors concluded that trials enrolling older participants show a small, statistically significant effect of HA on function and relatively few serious AEs; however no studies limited participation to those 65 years or older. No conclusions can be drawn from the available literature on delay or avoidance of total knee replacement through the use of HA. Studies that can compare large numbers of treated and untreated individuals, preferably with a randomized design, are needed to answer this question (2015).

Unproven

Temporomandibular Joint (TMJ)

One treatment for TMJ disorders is the injection of substances into the joint to replace synovial fluid. Hyaluronates are one class of synovial fluid replacements. These substances are purified natural substances that have been shown to improve the pain associated with TMJ disorders.

Sodium hyaluronate has not been labeled by the FDA for use in the TMJ. Some evidence from RCTs indicates that this treatment may have a beneficial effect in patients with OA or disc disorders of the TMJ. However, evidence has largely been found to be insufficient, generally concluding that additional research is necessary to draw clinically useful information.

A systematic review by Manfredini et al. (2010) aimed to summarize and systematically review the clinical studies evaluating the use of hyaluronic acid injections to treat TMJ disorders. 19 studies were selected for review, twelve of which addressed the use of hyaluronic acid in TMJ disk displacements, and seven of which dealt with inflammatory-degenerative disorders. Based on the available literature, the authors found that few randomized and controlled trials comparing the effectiveness of HA injections with that of other treatments have been performed, with only nine research groups accounting for more than half of the available published literature, thus limiting generalization of findings. Based on the findings, the authors concluded that despite effectiveness seen in case series, sodium hyaluronate injections did not prove superior to other active treatments, such as corticosteroid injections or occlusal appliances. The authors indicate that significant additional study is required to better identify appropriate indications and dosing regimens.

A systematic review by Goiato et al. aimed to investigate whether IA injections of HA were better than other drugs used in TMJ arthrocentesis, for the improvement of temporomandibular disorder (TMD) symptoms. Selected studies were RCTs and prospective or retrospective studies that primarily investigated the application of HA injections compared to other IA medications for the treatment of TMD. The initial screening yielded 523 articles, of which 8 were selected and fulfilled the inclusion criteria. Results of the review identified that IA injections of HA are beneficial in improving the pain and/or functional symptoms of TMDs. However, other drug therapies, such as corticosteroid and non-steroidal anti-inflammatory drug injections, can be used with satisfactory results. Well-designed clinical studies are necessary to identify an adequate protocol, the number of sessions needed, and the appropriate molecular weight of HA for use (2016).

Moldez et al. (2017) performed a systematic review and meta-analysis to assess the effectiveness of intra-articular injections of sodium hyaluronate or corticosteroids for treatment of intracapsular TMD. Selected studies were single or double-blinded RCTs compared to each other or placebo. Screening yielded 250 studies, of which 22 were identified as relevant, but only 7 RCTs met the inclusion criteria. Pooled results showed no significant difference in short- or long-term pain improvement with sodium hyaluronate compared to corticosteroid IA injections. The authors concluded that further research is needed to determine the minimum effective dose and long-term side effects of both injections.

Gokçe et al. (2019) conducted a RCT to comparatively evaluate the use IA corticosteriods, sodium hyaluronate, and platelet-rich plasma in those with TMJ pain and clinically diagnosed with TMJ-osteoarthritis. A total of 60 patients evaluated in 2 groups as those patients who felt pain on lateral (N = 31), and posterior (N = 43) palpation. They were then randomly assigned to 3 different treatment groups who underwent IA injection with either corticosteriods, sodium hyaluronate, or platelet-rich plasma, who were assessed for pain felt on the TMJ on lateral and posterior palpation before treatment and every month for 4 months using a 5-point pain scale. Presence of crepitation, loss of function, and loss of strength were also assessed before treatment and every month for 3 months. Authors found that while all three treatment modalities showed significant improvement in clinical pain scores, the most improvement was found in the platelet-rich plasma group and decreased TMJ palpation pain more effectively compared to the sodium hyaluronate and corticosteroid groups.

Shoulder

Zhang and colleagues (2019) conducted a systematic review and meta-analysis to evaluate the efficacy of HA for pain reduction in patients with glenohumeral OA. Electronic and manual search produced 1392 articles, of which 31 were eligible for full-text review. From the 31, 15 met all inclusion criteria, enrolling a total of 1594 patients. Primary outcome was change in VAS for pain, and secondary outcomes were functional outcome and AEs. In the HA arm, VAS scale reduction at 3 and 6 months was 26.2 mm and 29.5 mm, respectively. All studies reported an improvement in functional outcome. Similar clinical improvements were reported in the intervention and control groups, suggesting that these improvements may not be directly related to HA. AEs were rare and included swelling and mild pain at the injection site, local effusion, lethargy, and face rash. The study

concluded that IA HA injection is safe and improves pain for patients with glenohumeral OA. Pain improvements also reported in the control group suggest that a significant placebo effect may be present with respect to IA shoulder injection. Further RCTs are necessary to evaluate the efficacy of HA and identify optimal dosing and route of administration.

A systematic review was performed to document potential benefit and AEs of HA injection into the shoulder with rotator cuff (RC) tears. The review included a total of 11 prospective and 7 randomized studies, clinically evaluating 1102 patients after different HA injections compared with corticosteroid injection, PT, saline solution injection and control groups. The authors concluded that while IA injections of HA are effective to reduce pain and improve the function of the shoulder in patients with RC pathology with no severe complications or AEs, further RCTs are necessary (Osti et al., 2016).

A double-blind, placebo RCT by Chou et al. (2010) evaluated the use of sodium hyaluronate in 51 patients with RC lesions without complete tears. Patients received either weekly injections of sodium hyaluronate or normal saline for 5 weeks. Outcomes were measured using a Constant score, which measures shoulder function, and VAS. The Constant score and VAS improved every week throughout treatment for both groups. However the treatment group showed greater improvement. The authors concluded that subacromial injections of sodium hyaluronate may be an alternative treatment in patients with RC lesions. The study is limited by small sample size and lack of comparison to other treatments such as subacromial steroid injection.

A prospective study by Brander et al. (2010) evaluated the use of 2 IA injections of Hylan G-F 20 in 36 patients with shoulder arthritis who had failed 3 months of standard treatment. After injection, patients had equal or greater than 20% improvement in VAS scores. Seven patients reported either increased pain (N = 3) at 6 months or no pain relief (N = 4). Despite these results, the authors concluded that 2 injections of Hylan G-F 20 should be considered for treating shoulder arthritis. The study is limited by small sample size and lack of comparison to a control group.

For OA of the shoulder, a meta-analysis of 2120 patients from 19 RCTs reported significant improvement in pain and functional scores, but not shoulder range of motion (ROM), after IA HA injection. In comparison with steroid injection, improvement was modestly better, but the authors were concerned with significant heterogeneity and other quality issues across all studies. They recommended that additional studies be performed (Saito et al., 2010).

A nonrandomized study of 93 elderly patients with cuff tear arthropathy of the shoulder found that in the 33 patients receiving IA HA, pain scores were significantly improved during the first 4 months as compared with the control group. The groups were equivalent after 5 months. The authors indicate that further study is required (Tagliafico et al., 2011).

While use of HA in the shoulder has been approved by the European Medicines Agency since 2007, the FDA has approved its use only in knees (Kwon et al., 2013).

A double-blind, placebo RCT titled “Comparative Analysis of Intra-articular Injection of Steroid and/or Sodium Hyaluronate in Adhesive Capsulitis” was completed in December 2013. To date, no study results have been posted. Additional information is available at: www.ClinicalTrials.gov. (Accessed June 3, 2019)

Overall, the limited evidence from these studies suggests that IA injection of sodium hyaluronate has promise for relieving shoulder pain and improving function and QOL in patients with shoulder OA. However, additional studies are necessary.

Hip

Migliore et al. (2014) studied an innovative visco supplement produced with a high concentration of both HA and sorbitol and evaluated its success with mid-term pain relief in symptomatic hip OA. A total of 20 patients were enrolled in the study and received one IA ultrasound (US)-guided injection of two syringes of Synolis V-A (ANTI-OX-VS, Canada) into the target hip. Lequesne index, Health Assessment Questionnaire (HAQ), pain reduction, Global Patient Assessment, Global Medical Assessment and reduction in monthly analgesic consumption were assessed during the 12-month post-injection follow-up period. Eleven drop-out patients were registered, of whom 2 were for loss of efficacy at 6 months, 1 for loss of efficacy at 9 months, and 8 patients for severe comorbidities. Mean scores of all clinical parameters evaluated at each control visit were significantly different when compared with baseline mean value, and no systemic AEs were observed. Even though the sample size of this study was limited, the researchers concluded that the results suggest a durable good efficacy of a single 4-ml injection of ANTI-OX-VS in hip OA, at least for the patients who completed the study. A larger number of patients and an RCT are needed.

A retrospective review on 224 participants who received injections of hylan G-F 20 and subsequently were followed to see if total hip replacement (THR) was required was conducted by Migliore and colleagues. Of the study participants, 56 were classified as being candidates for THR and 168 participants were classified to not be a candidate. Following injections, 84 participants later required THR (32 of these participants came from the non-surgical candidate group). Survival time (in months) was the amount of time between start of treatment with injections and THR, if performed. Twelve month survival was achieved by 206 participants, 24 month survival was achieved by 170 participants, and 5 year survival was achieved by 69 participants. This study was limited by its retrospective design and lack of a control group. The authors noted that IA treatment is known to have a placebo effect, and additional studies are needed to gain further insight into functional and clinical improvement (2012).

A multicenter, placebo RCT was conducted by Richette et al. (2009) on 85 patients with symptomatic hip OA (pain score of > 40 mm on a VAS and a Kellgren/Lawrence grade of 2 or 3). Patients were randomized to the HA group (N = 42) or placebo group (N = 43) and followed for 3 months. At 3 months, the decrease in pain score did not differ between the HA and placebo groups in the intent-to-treat analysis. The authors concluded that a single IA injection of HA is no more effective than placebo in treating the symptoms of hip OA.

Migliore and colleagues (2009) conducted a prospective double-blind trial of 42 patients with OA of the hip, comparing2 monthly injections of IA bacterial-derived HA (Hyalubrix®, Hymovis in the US) with local analgesia (mepivacaine). Outcomes were measured by the Lequesne algo functional index (grades 1 to 4), VAS, and the patient's global assessment score. Both groups showed improvement from baseline; however, the HA group showed greater improvement in Lequesne algo functional index and VAS scores. The authors concluded that IA HA may be a treatment option for patients with OA of the hip. The study is limited by small sample size and lack of a control group.

Use of HA has been approved in Europe for hip pain. However, no clinical trials are in progress in the U.S. relating to viscosupplementation and OA of the hip.

The U.S. Department of Veterans Affairs and the U.S. Department of Defense (VA/DoD) clinical practice guidelines for the non-surgical management of hip and knee OA state that IA injection of hyaluronate/hylan is not recommended for patients with symptomatic OA of the hip (2014).

Ankle Osteoarthritis

A study by Mei-Dan et al. (2010) evaluated the efficacy of sodium hyaluronate to treat ankle OA in 16 patients. Patients underwent 5 weekly injections and were followed for 32 weeks. Improvement in pain was seen in 13 of the 15 patients for the duration of the study. One patient was dropped from follow-up due to unrelated surgery. ROM improved by 20%, and there was a reduction in pain assessed by VAS and ankle-hindfoot scores. The authors concluded that IA injection of sodium hyaluronate for ankle OA is a viable treatment option. The study was limited by small sample size, lack of a control group and lack of baseline data for ROM and pain.

A case series of 51 patients with OA of the ankle demonstrated improvement in pain, function, and balance at 6-month follow-up after 3 weekly IA HA injections; however, the authors advised that larger controlled trials with longer follow-up are needed (Sun, 2011). A randomized study with 26 patients assigned to HA at 3 different single doses, or to 3 weekly injections of the lowest dose, found that after 15 weeks only those receiving 3 weekly injections had significant improvement in pain score, but there was no placebo group and the study suffered from a high dropout rate in several groups (Witteveen, 2010). A subsequent review found that while use of HA for ankle arthritis continues to be actively investigated, there has not been confirmation of effectiveness or determination of established dosing regimens, and significant additional study is required (Migliore, 2011). A double-blind placebo RCT of 64 patients with ankle OA found that there was no significant difference in effectiveness between treatment with a single IA injection of HA vs saline solution at both 6- and 12-week follow-up (DeGroot, 2012).

A Cochrane review assessed the benefits and harms of any conservative (non-surgical) treatment for ankle OA in adults. Six RCTs were included. The primary analysis included three RCTs which compared HA to placebo (109 participants). One study compared HA to exercise therapy (N = 30), one compared HA combined with exercise therapy to an IA injection of botulinum toxin (N = 75), and one compared four different dosages of HA (N = 26). The outcomes from each study were graded as low quality due to limitations in study design and clinical significance of results secondary to small population size in each study group. The authors concluded that currently, there is insufficient data to create a synthesis of the evidence as a base for future guidelines for ankle OA. Since the etiology of ankle OA is different, guidelines that are currently used for hip and knee OA may not be applicable (Witteveen et al., 2015).

A 2014 guidance document from the National Institute for Health and Care Excellence (NICE) states that IA hyaluronan injections should not be offered for the management of OA.

Rheumatoid Arthritis (RA)

There is controversy regarding the underlying biological basis for use of sodium hyaluronate for the treatment of RA. There is some evidence that sodium hyaluronate inhibits synovial cell proliferation and suppresses lymphocyte proliferation, both of which occur in RA patients (Matsuno, 1999). Furthermore, sodium hyaluronate has been shown to inhibit the release of proteoglycans from articular cartilage, a finding that suggests that there may be a reduction in degeneration of the cartilage (Matsuno, 1999). In patients with OA, sodium hyaluronate increases the viscoelasticity of synovial fluid, which plays a key role in cushioning and protecting the joint. However, an increase in viscoelasticity of synovial fluid after sodium hyaluronate injection has not been demonstrated in patients with RA, and it has not been determined whether sodium hyaluronate is protective in joints affected by RA. Wang (2002) concluded that glycosaminoglycans (HA) may be a potential cause of RA. Majeed (2004) found that the high HA levels correlated with early RA disease activity.

Wang and associates (2017) studied patients with unilateral or bilateral ankle and foot RA to determine whether HA injection can improve foot function and reduce synovial hyper-vascularization using a pilot RCT. All the patients (44 individuals, 75 ankles and feet) were randomized to receive HA (N = 40) or lidocaine injection (LI) (N = 35) at 2-week intervals. Clinical assessments were performed using a VAS and foot function index (FFItotal) including subscales of pain (FFIpain) prior to injection at baseline, at 4 weeks (first evaluation) and at 12 weeks (secondary evaluation). Imaging evaluation based on color Doppler ultrasound (CDUS) and synovitis scores was performed simultaneously. HA injection improved the VAS score, FFIpain, and FFItotal considerably more than LI injections did at the first evaluation. The CDUS values at first and secondary evaluation decreased significantly compared with baseline. HA injections reduced the CDUS values of more than half of the joints (54%) while the control group exhibited no change (20%). However, HA injection did not reduce the CDUS values more than LI injection did. Regarding the evaluation of synovial hypertrophy, no significant difference was observed between or within the groups. The authors concluded that HA injection improved short-term foot function, reduced pain, and may have a modest effect in reducing synovial hyper-vascularization. Further large-scale studies are warranted to confirm these results.

For RA of the knee, a meta-analysis found 5 RCTs with 720 patients that, when pooled, resulted in significant effect sizes in favor of HA in terms of improvement of pain and inflammation, as well as overall treatment effectiveness. However, the authors cautioned that the number and sizes of studies were small, and that several sources of bias were present, such as with regard to language, type of preparation used, and conflicting results from larger vs smaller studies. The authors urged that additional large RCTs be undertaken (Saito and Kotake, 2009).

Joint Replacement

There are no clinical trials evaluating the use of sodium hyaluronate in persons following total or partial joint replacement surgery.

Glottic (Vocal Cord) Insufficiency/Incompetence

Pei et al. (2015) conducted an open-label, RCT, investigating the neurologic and functional effect of intracordal hyaluronate injections in 29 patients with acute unilateral vocal fold paralysis (UVFP). Participants were recruited within 6 months of their first outpatient visit and were randomized to receive either single hyaluronate injection (HI group) or conservative management (CM group). Quantitative laryngeal electromyography (LEMG), videolaryngostroboscopy, UVFP-related QOL Voice Outcomes Survey (VOS), laboratory voice analysis, and health-related QOL (SF-36) were evaluated at baseline, and at 1, 3 and 6 months post-injection in the HI group, and at baseline and 6 months in the CM group. Improvements in most QOL domains and other assessments were comparable between groups; however, the HI group had a greater improvement in the mental health domain of QOL at the end of follow-up. The authors concluded that early hyaluronate injection cannot improve nerve regeneration but can result in long-lasting improvements in patients' psychosocial well-being, thus highlighting the importance of early intervention for patients with UVFP.

Wang et al. (2015) conducted a prospective single institution study of the long-term treatment results from 74 patients who received LEMG-guided HA vocal fold injection laryngoplasty (IL) for UVFP from March 2010 to February 2013. Participants were injected with 1.0 mL of HA via LEMG guidance in the office setting. Outcome measures included various glottal closure evaluations such as normalized glottal gap area, maximal phonation time, phonation quotient, mean airflow rate, perceptual GRBAS (grade, roughness, breathiness, asthenia, strain) scale, and Voice Handicap Index (VHI). Measures were compared

before and after injection using the nonparametric Wilcoxon signed rank test within 1 month, at 6 months, and at the last follow-up examination. Sixty patients had been followed for at least 6 months, 44 patients received only 1 injection, and 16 patients received either 2 or 3 injections. All the glottal closure parameters improved significantly within 1 month, at 6 months, and at the last follow-up examination, with a mean of 17.4 months. At the last follow-up examination, all outcome parameters were significantly improved. The authors concluded that of the 74 patients in this study, 44 (60%) who received a single injection and 16 (22%) who received multiple injections did not require another treatment after long-term follow-up. LEMG-guided HA vocal fold injection is an option for treating UVFP with satisfactory results. Limitations include small study size and lack of comparison with other injectable agents.

Lau et al. (2010) conducted a prospective single-blind RCT to determine if particle size affects durability of medialization in patients undergoing IL with HA for unilateral vocal cord paralysis (UVCP). Patients underwent the procedure in the office setting with Restylane (small particle-size HA, SPHA) or Perlane (large particle-size HA, LPHA) (Q-Med AB, Uppsala, Sweden). The VHI at 6 months post-injection was the primary outcome measure. Secondary outcomes included video stroboscopic findings and objective acoustic and aerodynamic measures. The study included 41 initial participants but follow-up data was available for only 17 patients after 6 months (8 SPHA, 9 LPHA). Normalized VHI scores at 6 months post-injection were significantly lower in the LPHA group compared to the SPHA group when not adjusted for age and sex. After adjustment, the difference was not significant, but the LPHA group trended toward lower normalized VHI scores. The findings support the authors' hypothesis that the LPHA product makes this material more durable. This material may be considered for temporary medialization in patients with UVCP in whom medium-term improvement of at least 6 months is desirable.

A Cochrane review by Lakhani et al. assessed the effectiveness of alternative injection materials in the treatment of UVFP. Authors identified no RCTs which met the inclusion criteria. Excluded were 18 studies on methodological grounds: 16 non-randomized studies; one RCT due to inadequate randomization and inclusion of non-UVFP patients; and one RCT which compared two different particle sizes of the same injectable material. The authors concluded that there is currently insufficient high-quality evidence for or against specific injectable materials for patients with UVFP. Future RCTs should aim to provide a direct comparison of the alternative materials currently available for injection medialization (2012).

Gotxi-Erezuma, et al. (2017) studied the effectiveness of EMG-guided HA IL in 28 patients in the early stage of UVFP, assessing patient recovery from dysphonia and QOL. Outcome measures included the VHI, GRBAS, video stroboscopic parameters and maximum phonation time assessed before, 15 days and 6 months after the intervention, using the non-parametric Wilcoxon rank test. Out of the 28 patients, 1 experienced a hematoma in the injected vocal fold and 6 required second injections. All outcome parameters were significantly improved at both 15 days and 6 months post-intervention. The authors concluded that EMG-guided HA IL in UVFP enables, in the same intervention, neuromuscular assessment and temporary treatment of glottic insufficiency with a low risk of complications and improvement in patient's QOL. Further research is required to confirm whether this may reduce the need for subsequent treatments.

Miaśkiewicz et al. (2016) performed a study on 39 individuals with dysphonia to assess the quality of voice over the long term when treated with HA injection into the vocal fold. The study group included patients with presbyphonia, scar, sulcus, UVFP and atrophy of the vocal fold. Patients' voice was assessed using the subjective GRBAS scale, and the objective Multidimensional Voice Program (MDVP). All patients underwent IL with HA into the vocal folds. Follow-up examinations were conducted at 6, 12 and 24 months postoperatively. Perceptual voice quality assessed with the GRBAS reflected improvement; and the MDVP showed a significant statistical improvement within the group of frequency, amplitude and noise parameters. The authors concluded that HA injection into the vocal fold improves the quality of voice in patients suffering from glottic insufficiency.

When discussing techniques and product choices for IL, Salinas and Chhetri describe Restylane and Hylan b Gel as durable cross-linked preparations with a viscoelastic profile that most closely resembles that of the human vocal fold. They state that results may last approximately 4–6 months, but also state that the use of either product in the larynx is considered off label (2014).

Treatment of Skin Contours and Depressions

While sodium hyaluronate can fill in contours, the presence of depressions and/or wrinkles is not a functional impairment. Use of sodium hyaluronic gel for these indications is cosmetic.

Professional Societies

American College of Rheumatology (ACR)

In its published "Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee," the ACR makes both "strong" and "conditional" recommendations for OA management. The ACR states that in OA generally, IA glucocorticoid injection is conditionally recommended over other forms of IA injection, including hyaluronic acid preparations. Head-to-head comparisons are few, but evidence for efficacy of glucocorticoid injections were considerably higher quality than that of other agents.

They also stated that IA hyaluronic acid injections are conditionally recommended against in patients with knee and/or first CMC joint OA, as best evidence failed to establish a benefit, and that harm may be associated with these injections. However, as many providers want the option of using hyaluronic acid injections when other interventions fail to adequately control local joint symptoms in clinical practice, the ACR recommends that using hyaluronic acid may be viewed more favorably than offering no intervention, and therefore may be used in the context of shared decision-making that recognizes the limited evidence of benefit of this treatment.

In contrast, the ACR strongly recommended against use in patients with hip OA due to higher quality evidence of lack of benefit (2020).

American Academy of Orthopaedic Surgeons (AAOS)

In their 2nd edition evidence based guideline titled "Treatment of Osteoarthritis of the Knee," the AAOS does not support the use of viscosupplementation for treatment of knee OA. This rationale is based on limitations in the literature which include variable quality of studies, a large degree of heterogeneity in outcomes, and possible publication bias (2013).

In the AAOS 3rd edition evidence based guideline titled "Treatment of Osteoarthritis of the Knee," hyaluronic acid intra-articular injection(s) is not recommended for routine use in the treatment of symptomatic osteoarthritis of the knee.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Osteoarthritis

Sodium hyaluronate has been approved and is marketed as a device for IA treatment of pain due to OA of the knee because it acts mechanically, as a lubricant, rather than by absorption into the body as would a drug.

A number of different HA preparations used for viscosupplementation have been approved as devices through the FDA Premarket Approval (PMA) process. They are all classified under the same Product Code, MOZ, which is identified in the FDA database as "acid, hyaluronic, intraarticular."

The FDA has approved the following labeling instructions as single-treatment regimens in patients who have failed conservative therapy with exercise and simple analgesics:

- Durolane: Approved as a single injection
- Euflexxa: Approved for 3 injections
- Gel-One: Approved as a single injection
- Gelsyn-3: Approved for 3 injections
- GenVisc 850: Approved for 3-5 injections
- Hyalgan: Approved for 5 injections
- Hymovis: Approved for 2 injections
- Monovisc: Approved as a single injection
- Orthovisc: Approved for 3-4 injections
- Supartz: Approved for 3-5 injections
- Synojoynt: Approved for 3 injections
- Synvisc One: Approved as a single injection
- Synvisc: Approved for 3 injections

- Triluron: Approved for 3 injections
- TriVisc: Approved for 3 injections
- Visco-3: Approved for 3 injections

Contraindications

- Do not administer to patients with known hypersensitivity (allergy) to hyaluronate preparations or allergies to avian or avian-derived products (including eggs, feathers, or poultry). This contraindication does not apply to Orthovisc.
- Do not administer to patients with known hypersensitivity (allergy) to gram positive bacterial proteins. This contraindication applies to Orthovisc only.
- Do not inject sodium hyaluronate into the knees of patients with infections or skin diseases in the area of the injection site or joint.

Skin Contouring (Including Acne, Scars and Wrinkle Treatments)

The FDA has approved several products containing a transparent HA gel to improve the contours of the skin. These products are used to treat acne, scars and wrinkles on the skin by temporarily adding volume to facial tissue and restoring a smoother appearance to the face. Devices include:

- Restylane injectable gel received PMA approval March 25, 2005
- Perlane® injectable gel received PMA approval May 2, 2007
- Hylaform received PMA approval April 22, 2004
- Juvéderm 24HV, Juvéderm 30 & Juvéderm 30HV Gel Implants received PMA approval June 2, 2006

Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determination (NCD) for intra-articular injections of sodium hyaluronate (Durolane®, Euflexxa®, Gelsyn-3™, Hyalgan®, Hymovis®, Gel-One®, GenVisc 850®, Monovisc™, Orthovisc®, Supartz™, Synojoynt™, Synvisc®, Synvisc-One®, Triluron™ ,TriVisc™ and Visco-3™). Local Coverage Determinations (LCDs) and Local Coverage Articles (LCAs) exist. Refer to the LCDs for Hyaluronan Acid Therapies for Osteoarthritis of the Knee, Hyaluronic Acid Injections for Knee Osteoarthritis and Viscosupplementation Therapy For Knee. Also refer to the LCAs for Hyaluronans Intra-articular Injections of and Intraarticular Knee Injections of Hyaluronan.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed April 6, 2023)

**Preferred therapy criteria for Medicare Advantage members, refer to Medicare Part B Step Therapy Programs.

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Policy History/Revision Information

Date	Summary of Changes
06/01/2023	**Supporting Information** • Updated *Clinical Evidence*, *CMS*, and *References* sections to reflect the most current information • Archived previous policy version 2022D0081G

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.