

SODIUM HYALURONATE

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[Instructions for Use](#) ⓘ

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Related Commercial Policies

- [Autologous Chondrocyte Transplantation in the Knee](#)
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Community Plan Policy

- [Sodium Hyaluronate](#)

COVERAGE RATIONALE

The following are proven and medically necessary:

- Intra-articular injections of sodium hyaluronate when administered according to U.S. Food and Drug Administration (FDA) labeled indications for treating pain due to:
 - Knee osteoarthritis (OA)
 - Temporomandibular joint osteoarthritis
 - Temporomandibular joint disc displacement
- Repeated courses of intra-articular hyaluronan injections may be considered when **all** of the following are met:
 - 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.

FDA Labeling*

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

*Hyaluronic acid preparations for the treatment of pain due to OA of the knee are deemed therapeutically equivalent. The UnitedHealth Group National Pharmacy and Therapeutics Committee has defined as therapeutically equivalent, products that can be expected to produce essentially the same therapeutic outcome and toxicity.

Intra-articular injections of sodium hyaluronate are unproven and not medically necessary for treating any other indication not listed above as proven due to insufficient evidence of efficacy.

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.

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 Coverage Determination 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

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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

ICD-10 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

ICD-10 Diagnosis Code	Description
M17.9	Osteoarthritis of knee, unspecified
M26.69	Other specified disorders of temporomandibular joint
M26.601	Right temporomandibular joint disorder, unspecified
M26.602	Left temporomandibular joint disorder, unspecified
M26.603	Bilateral temporomandibular joint disorder, unspecified
M26.609	Unspecified temporomandibular joint disorder, unspecified side
M26.611	Adhesions and ankylosis of right temporomandibular joint
M26.612	Adhesions and ankylosis of left temporomandibular joint
M26.613	Adhesions and ankylosis of bilateral temporomandibular joint
M26.619	Adhesions and ankylosis of temporomandibular joint, unspecified side
M26.621	Arthralgia of right temporomandibular joint
M26.622	Arthralgia of left temporomandibular joint
M26.623	Arthralgia of bilateral temporomandibular joint
M26.629	Arthralgia of temporomandibular joint, unspecified side
M26.631	Articular disc disorder of right temporomandibular joint
M26.632	Articular disc disorder of left temporomandibular joint
M26.633	Articular disc disorder of bilateral temporomandibular joint
M26.639	Articular disc disorder of temporomandibular joint, unspecified side

DESCRIPTION OF SERVICES

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 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, 2017). 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 non prescription 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 intra-articular hyaluronan product is superior to another.

CLINICAL EVIDENCE

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.

Knee Osteoarthritis

A systematic review and meta-analysis by Bannuru et al. (2009) compared the effectiveness of intra-articular 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 intra-articular 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 effectiveness 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 intra-articular injection of hylan G-F 20 (n=123) with placebo (n=130) in patients with symptomatic knee OA. Outcomes were measured by the Western Ontario and McMaster Universities (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 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 intra-articular 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 intra-articular injection series with Suplasyn 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 intra-articular HA as an effective long-term therapeutic option for patients with OA of the knee.

Conrozier et al. (2009) conducted a prospective, multi-center, randomized study of 100 patients to evaluate the safety and efficacy of five dosing regimens of viscosupplementation with hylan G-F 20 in patients with symptomatic tibio-femoral OA. Patients were randomized to receive varying dosing regimens of hylan G-F 20 (1 x 6 mL, 1 x 4 mL, 2 x 4 mL 2 weeks apart, 3 x 4 mL 1 week apart, or 3 x 2 mL 1 week apart). Patients in the 3 x 4 mL group reported the highest percentage of device-related local adverse events (AEs) (30%) while patients in the 1 x 6 mL and 3 x 2 mL groups reported only 10%. Patients in the 1 x 6, 3 x 4 and 3 x 2 mL treatment groups showed the greatest improvements in the patient-rated knee OA pain assessment VAS. The authors concluded that a single 6 mL injection of hylan G-F 20 may be as efficacious, and as well tolerated, as 3 x 2 mL one week apart; however, a double-blind, controlled trial is needed to confirm these data.

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-analysis 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 intra-articular 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 intra-articular injections of bioengineered hyaluronate given 23 weeks after the initial 3-injection treatment course was safe and effective for symptom relief (Altman, 2011).

Comparative trial reported no significant differences among 3 different HA formulations: Orthovisc, Synvisc, and Ostenil (Juni et al., 2007). This was a multicenter, patient-blind, RCT in 660 patients with symptomatic knee OA. Patients were randomly assigned to receive 1 cycle of 3 intraarticular injections per knee of 1 of 3 preparations: a high molecular weight cross-linked hylan, a non-cross-linked medium molecular weight HA of avian origin or a non-cross-linked low molecular weight HA of bacterial origin. 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 pain relief was similar in all 3 groups. The difference in changes between baseline and 6 months between hylan and the combined HAs was 0.1 on the WOMAC pain score (95% confidence interval). No relevant differences were observed in any of the secondary efficacy outcomes, and stratified analyses provided no evidence for differences in effects across different patient groups. There was a trend toward more local AEs in the hylan group than in the HA 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 evidence for a difference in efficacy between hylan and the 2 HAs.

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 Sinvisc. 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 intra-articular 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 Sinvisc were equally effective.

A systematic review conducted under contract by AHRQ evaluated 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 (Newberry et al. 2015).

Temporomandibular Joint

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.

Although sodium hyaluronate has not been labeled by the FDA for use in the TMJ, the evidence from RCTs indicates that this treatment has a beneficial effect in patients with OA or disc disorders of the TMJ.

In a systematic review, Machado et al. (2013) analyzed the effectiveness of intra-articular injections with corticosteroids and sodium hyaluronate for treating internal derangements of the TMJ. Nine articles were collected, 7 of which were double-blind RCTs and 2 single-blind RCTs. After analyzing the literature, it was found that intra-articular injection with corticosteroids and sodium hyaluronate seems to be an effective method for treating internal derangements of the TMJ.

Gencer et al. (2014) performed a comparative study of 100 patients diagnosed with TMJ disorder, examining efficacy of intra-articular injections of 3 different agents with well known anti-inflammatory properties. In the study group there were 55 female and 45 male patients who were non-responders to conventional anti-inflammatory treatment for TMJ complaints. The patients were randomly divided into 4 groups consisting of a control group and 3 different groups who underwent intra-articular injection of one given anti-inflammatory agent for each group. The control group was injected with saline solution into the intra-articular space. The others were divided into 3 groups & received either HA (Hyalgan intra-articular injection), betamethasone, or tenoxicam. Following the completion of injections, the changes in subjective symptoms were compared with VAS scores at follow up visits at 1 and 6 weeks respectively. The authors concluded that HA produced better pain relief scores when compared to the other anti-inflammatory agents studied.

Long et al. (2009) conducted a RCT on 120 patients to compare the outcome of inferior and superior joint space injection of sodium hyaluronate in patients with disc displacement without reduction of the TMJ. Patients were randomized into 2 experimental groups. One group of patients received superior joint space injections of sodium hyaluronate and the other group was treated with inferior joint space injections. Patient's TMJ status and clinical symptoms were evaluated at the 3 and 6 month follow-up appointments. The clinical parameters recorded were maximal mouth opening (MMO), pain intensity on a VAS, and modified Helkimo's clinical dysfunction index and analyzed with ANCOVA. Fifty of the superior and 54 of the inferior joint space injection therapy group returned for the 3 and 6 month evaluations. Both groups had improvement in the clinical parameters at the 3 and 6 month follow-ups; however, the inferior joint injection group at 3 months had a greater reduction in TMJ pain compared with the superior joint injection group. The authors concluded that inferior joint space injection with sodium hyaluronate is a valid method of treating disc displacement without reduction of TMJ and a long-term study will be needed to assess the effect of inferior joint injection on the morphologic changes of the TMJ.

Shoulder

A systematic review was performed to document potential benefit and AEs of HA injection into the shoulder with rotator cuff 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 intra-articular injections of HA are effective to reduce pain and improve the function of the shoulder in patients with rotator cuff pathology with no severe complications or AEs, further RCTs are necessary (Osti et al., 2016).

Hayes conducted evidence review on viscosupplementation for shoulder OA in adults using non-cross-linked sodium hyaluronates. These include 2 multicenter, double-blind, placebo RCTs (n=300 to 660), and 1 prospective cohort study (n=27). Sodium hyaluronates investigated included Supartz, Hyalgan, and Euflexxa. All of the studies had manufacturer funding. All 3 studies used varying dosing schedules of the sodium hyaluronates: Supartz was administered as 3 weekly injections over a 3-week period, Hyalgan as 3 or 5 weekly injections, and Euflexxa as 1 weekly injection for each of 3 weeks. All of the studies followed patients for approximately 26 weeks. Some studies included patients with shoulder comorbidities such as rotator cuff tear or adhesive capsulitis. The primary outcome measure in all 3 studies was shoulder pain measured by a VAS. A variety of secondary outcomes were assessed using several other validated tools that assess, for example, functioning and quality of life (QOL) in patients with shoulder pain. It was concluded that there is insufficient evidence to determine the optimal patient selection criteria for these viscosupplements for treatment of persistent and disabling pain due to shoulder OA. There is a need for additional trials to further evaluate the efficacy and safety of these agents, which include comparisons with other therapies. Long-term studies with follow-up times longer than 6 months are needed to evaluate treatment durability since OA is a chronic condition (2014, updated 2016).

A double-blind, placebo RCT by Chou et al. (2010) evaluated the use of sodium hyaluronate in 51 patients with rotator cuff 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 rotator cuff 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 intra-articular 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 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, after intra-articular 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, and they recommended that additional studies be performed (Saito, 2010).

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

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 December 6, 2018)

Overall, the limited evidence from these studies suggests that intra-articular 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

A retrospective review by Migliore and colleagues (2012) reported on 224 participants who received injections of hylan G-F 20 and who were then followed to see if total hip replacement (THR) was required. Of the study participants, 56 were classified as being candidates for THR and 168 participants were classified to not be a candidate for a THR. 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 five year survival was achieved by 69 participants. This study is limited by its retrospective design and lack of a control group. The authors also note that intra-articular treatment is known to have a placebo effect and additional studies are needed to gain further insight into functional and clinical improvement.

A multicenter, placebo RCT by Richette et al. (2009) of 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 (mean +/- SD decrease 7.8 +/- 24.9 mm with HA versus 9.1 +/- 27.4 mm with placebo; P = 0.98). The authors concluded that the findings indicate that a single IA injection of HA is no more effective than placebo in treating the symptoms of hip OA.

A prospective double-blind trial by Migliore et al. (2009) of 42 patients with OA of the hip compared the use of intra-articular bacterial-derived HA (Hyalubrix[®]) with local analgesia (mepivacaine). Outcomes were measured by the Lequesne algofunctional index (grades 1 to 4), VAS, and the patient's global assessment score for hip OA. Patients receive 2 monthly injections. Both groups showed improvement from baseline. However, the HA group showed greater improvement in Lequesne algofunctional index and VAS scores. The authors concluded that intra-articular 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 NGC published the VA/DoD clinical practice guidelines for the non-surgical management of hip and knee OA. The guidelines state that intra-articular injection of hyaluronate/hylan is not recommended for patients with symptomatic OA of the hip (2014).

Ankle Osteoarthritis

Migliore et al. (2011) evaluated the effectiveness of viscosupplementation treatment of ankle OA in the current literature which included 7 articles and a total of 275 patients. The authors concluded that viscosupplementation is used widely in knee OA and is included in the professional guidelines for treatment of the disease in this joint. The potential for treating OA of the ankle joint by viscosupplementation has been suggested in the literature, however, no dosing studies have been published to date, and dosing in the ankle joint remains an area for discussion. They stated that viscosupplementation could potentially provide a useful alternative in treating such patients with painful ankle OA.

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. Range of motion improved by 20% and there was a reduction in pain assessed by VAS and ankle-hindfoot scores. The authors concluded that intra-articular injection of sodium hyaluronate for ankle OA is a viable treatment option. The study is limited by small sample size, lack of a control group and lack of baseline data for range of motion 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 of 3 weekly intra-articular 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 intra-articular injection of HA vs saline solution at both 6-week 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. No other RCT concerning any other conservative treatment besides the use of HA for ankle OA was identified. 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 intra-articular 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 for ankle OA (Witteveen et al., 2015).

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

Rheumatoid Arthritis

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.

Knee RA

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, 2009).

Patello-Femoral Syndrome or Chondromalacia

Review of the literature resulted in one study by Jiang et al. (2007) regarding the use of sodium hyaluronate for treatment of chondromalacia. This study was uncontrolled, and is insufficient to conclude that sodium hyaluronate is effective for treatment of chondromalacia. In the study, the researchers explored the use of sodium hyaluronate (visco-elastic material) for joint cavity filling combined with exercise for power in the treatment of chondromalacia patellae. The experiment was carried out among 179 knees of 120 patients with knee OA from April 2003 to May 2006. At the 90 degrees angle of knee flexion, the patella was injected with 2 mL sodium hyaluronate solution, once per week, and 5 times were taken as a course. Meanwhile, isometric exercise for strengthening medial vastus muscle was accompanied. The result showed that after 5-week exercise, the rate of excellent and good curative effects was 91.1%, and overall response rate reached 98.9%. Excellent: disappearance of knee joint pain and rigidity, free movement, knee joint flexion > 130 degrees and extension at 0 degrees in 102 knees; Good: basic disappearance of knee joint pain and rigidity, limited movement, knee joint flexion > 110 degrees and extension at 0 degrees in 61 knees; Fair: occasional disappearance of knee joint pain and rigidity, recovery after rest, limited movement, knee joint flexion 90 degrees and extension at 0 degrees in 14 knees; Ineffective: no improvements of knee joint pain and rigidity after injection, severely limited movement, knee joint flexion < 90 degrees and extension at 0 degrees in 2 knees.

The status of the RCT evaluating the efficacy of Synvisc-One® for the treatment of patellofemoral chondromalacia is unknown. Additional information is available at: www.clinicaltrials.gov. (Accessed December 6, 2018)

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 the HI and CM 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 (ClinicalTrials.gov [NCT02163772](https://clinicaltrials.gov/ct2/show/study/NCT02163772)). (Accessed December 6, 2018)

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) 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 up 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 videostroboscopic 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.

Hertegård et al. conducted a prospective trial to evaluate the long-term (24 months) clinical performance (vocal fold function) and safety of hylan B gel as compared with bovine cross-linked collagen in the treatment of individuals with glottal insufficiency. Seventy patients with glottal insufficiency due to UVFP (n =35) or atrophy (n =35) were randomized to receive either hylan B gel (n =47) or collagen (n =23) injections into 1 vocal fold. Forty-two of the patients were examined 24 months after treatment. Evaluations were made based on patients' subjective ratings, digitized videostroboscopic measurements, maximum phonation time and phonation quotient. The patients' self-ratings were significantly improved in both the hylan B gel and collagen groups. Videostroboscopic measurements of glottal closure were significantly improved for both groups. The hylan B gel group showed a trend towards less resorption at the injected vocal fold edge in comparison with the collagen group. No serious adverse events were observed. Twenty-eight patients dropped out of the study after 12 months: 18 had been re-injected or operated on with medialization laryngoplasty due to insufficient voice, and 10 had either died of causes unrelated to the study or refused to attend follow-up. The authors concluded that both injection treatments resulted in significantly improved voice as rated by the patients and significantly improved glottal closure with no long-term side-effects. Some resorption was noted for both substances, and approximately 25% of the patients chose re-treatment 2 years after the initial treatment (2004).

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. Outcomes measures included the VHI, GRBAS, videostroboscopic 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 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. Intraarticular hyaluronate injections were mentioned as being conditionally recommended in patients with knee OA. Recommendations for hip OA were similar to those for the management of knee OA. Intraarticular injections were not addressed in recommendations for OA of the hand (Hochberg, 2012).

American Academy of Orthopaedic Surgeons (AAOS)

In their 2nd edition evidence based guidelines 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).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Osteoarthritis

Sodium hyaluronate has been approved and is marketed as a device for intra-articular 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:

- Hyalgan: Approved for 5 injections
- Synvisc and Euflexxa: Approved for 3 injections
- Supartz: Approved for 3-5 injections
- Orthovisc*: Approved for 3-4 injections
- Synvisc One: Approved as a single injection
- Gel-One: Approved as a single injection
- Monovisc: Approved as a single injection
- Gelsyn-3: Approved for 3 injections
- GenVisc 850: Approved for 3-5 injections
- Hymovis: Approved for 2 injections
- Durolane: Approved as a single injection
- Visco-3: Approved for 3 injections
- TriVisc: Approved for 3 injections
- Synjoynt: 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.

Supartz received FDA approval on December 21, 2015. Additional information is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p980044s024. (Accessed December 6, 2018)

Synvisc-One (hylan G-F 20) received premarket approval February 26, 2009. Additional information is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p940015s034. (Accessed December 6, 2018)

Hyalgan® received FDA premarket approval on May 28; 1997. Additional information is available at: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P950027>. (Accessed December 6, 2018)

Gel-One (hyaluronan) received FDA premarket approval on March 22, 2011. Additional information is available at: http://www.accessdata.fda.gov/cdrh_docs/pdf8/p080020a.pdf. (Accessed December 6, 2018)

Orthovisc® High Molecular Weight Hyaluronan received FDA premarket approval on February 4, 2004. Additional information is available at: http://www.accessdata.fda.gov/cdrh_docs/pdf3/p030019a.pdf. (Accessed December 6, 2018)

Monovisc® received premarket approval February 25, 2014. Monovisc® is the first FDA approved single injection product comprised of HA which is derived from a non-animal source. Additional information is available at: http://www.accessdata.fda.gov/cdrh_docs/pdf9/P090031a.pdf. (Accessed December 6, 2018)

GelSyn™ (now known as Gelsyn-3) received FDA premarket approval on May 9, 2014. Additional information is available at:

- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p110005s001
- http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110005d.pdf

(Accessed December 6, 2018)

GenVisc 850® received FDA approval on September 2, 2015. Additional information is available at:

http://www.accessdata.fda.gov/cdrh_docs/pdf14/p140005b.pdf. (Accessed December 6, 2018)

Hymovis® received FDA approval on August 28, 2015. Additional information is available at:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p150010.

(Accessed December 6, 2018)

Durolane® received FDA approval on August 29, 2017. Additional information is available at:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P170007>. (Accessed December 6, 2018)

Visco-3 received FDA approval on December 21, 2015. Additional information is available at:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P980044S027>. (Accessed December 6, 2018)

TriVisc received FDA approval on November 13, 2017. Additional information is available at:

https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160057a.pdf. (Accessed December 6, 2018)

Synjoynt™ received FDA approval on May 8, 2018. Additional information is available at:

<https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm609709.htm>. (Accessed December 6, 2018)

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 used for treating pain due to osteoarthritis (OA) of the knee. Local Coverage Determinations (LCDs) exist; see the LCDs for [Hyaluronate Polymers](#), [Intra-articular Injections of Hyaluronan](#), [Hyaluronan Acid Therapies for Osteoarthritis of the Knee](#) and [Viscosupplementation Therapy for Knee](#).

Medicare does not have an NCD for intra-articular injections of sodium hyaluronate used for treating temporomandibular joint (TMJ) disorders. LCDs do not exist at this time.

(Accessed July 31, 2018)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
02/01/2019	<ul style="list-style-type: none">• Updated and reformatted coverage rationale:<ul style="list-style-type: none">○ Simplified content○ Added language to clarify hyaluronic acid gel preparations to improve the skin's <i>appearance</i>, contour and/or reduce depressions due to acne, scars, injury or wrinkles are considered cosmetic• Updated list of applicable ICD-10 diagnosis codes; removed coding clarification language• Updated supporting information to reflect the most current description of services• Archived previous policy version 2019T0078DD

INSTRUCTIONS FOR USE

This Medical 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, 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 Policy is provided for informational purposes. It does not constitute medical advice.

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