UnitedHealthcare Community Plan

UnitedHealthcare® Community Plan
Medical Benefit Drug Policy

SODIUM HYALURONATE

Policy Number: CSLA2020D0081B **Effective Date**: TBD

Instructions for Use

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APPLICATION

This Medical Benefit Drug Policy only applies to the state of Louisiana.

COVERAGE RATIONALE

Coverage for Durolane, Euflexxa, and Gelsyn-3 is contingent on criteria in the Diagnosis-Specific Criteria section.

- **Prior authorization is not required.**

Coverage for GenVisc 850, Hyalgan, Supartz, Visco-3, Hymovis, Orthovisc, Synvisc or Synvisc-One, Gel-One, Monovisc, TriVisc, or Synojoynt is contingent on Medical Necessity Criteria and Diagnosis-Specific Criteria.

- **In order to continue coverage, members already on these products will be required to change therapy to Durolane, Euflexxa, or Gelsyn-3 unless they meet the criteria below.**

Medical Necessity Criteria

Treatment with GenVisc 850, Hyalgan, Supartz, Visco-3, Hymovis, Orthovisc, Synvisc or Synvisc-One, Gel-One, Monovisc, TriVisc, or Synojoynt is medically necessary for the indications specified in this policy when ONE of the criteria below are met:

- **Both of the following:**
  - **History of a trial of adequate dose and duration of Durolane, Euflexxa, and Gelsyn-3, resulting in minimal clinical response; and**
  - **Physician attests that, in their clinical opinion, the clinical response would be expected to be superior than experienced with Durolane, Euflexxa, and Gelsyn-3**

or

- **Both of the following:**
  - **History of failure, contraindication, or intolerance to Durolane, Euflexxa, and Gelsyn-3; and**
  - **Physician attests that, in their clinical opinion, the same failure, contraindication, or intolerance would not be expected to occur with GenVisc 850, Hyalgan, Supartz, Visco-3, Hymovis, Orthovisc, Synvisc or Synvisc-One, Gel-One, Monovisc, TriVisc, or Synojoynt**

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: ~~**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~~Diagnosis of **one** of the following:
  - **Hip osteoarthritis**
  - Knee osteoarthritis ~~(OA)~~
  - Temporomandibular joint osteoarthritis
  - Temporomandibular joint disc displacement

  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 cannot be attributed to other forms of osteoarthritis; and**
  - **There are no contraindications to the injections (e.g., active joint infection, bleeding disorder); and**
  - **Dosing is in accordance with the U.S. FDA approved labeling as shown in the table below; and**
  - **Initial authorization is for a single injection course once per joint for 6 months**

Reauthorization/Continuation

Repeated courses of intra-articular hyaluronan injections may be considered when ~~all~~ ALL of the following are met:
- **Documentation of positive clinical response to therapy (e.g., significant pain relief was achieved with the prior course of injections); and**~~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 U.S. FDA approved labeling as shown in the table below; and**
- **Continuing authorization is for a single injection course once per joint for 6 months**

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

~~FDA Labeling*~~Sodium Hyaluronate Product	Course of Treatment per Joint
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
Synojoynt	3 injections
Synvisc	3 injections
Synvisc One	1 injection
TriVisc	3 injections

~~FDA Labeling*~~Sodium Hyaluronate Product	Course of Treatment per Joint
Visco-3	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 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 and are not covered.

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 federal, state or contractual requirements 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
M16.0	Bilateral primary osteoarthritis of hip
M16.10	Unilateral primary osteoarthritis, unspecified hip
M16.11	Unilateral primary osteoarthritis, right hip
M16.12	Unilateral primary osteoarthritis, left hip
M16.2	Bilateral osteoarthritis resulting from hip dysplasia
M16.30	Unilateral osteoarthritis resulting from hip dysplasia, unspecified hip
M16.31	Unilateral osteoarthritis resulting from hip dysplasia, right hip
M16.32	Unilateral osteoarthritis resulting from hip dysplasia, left hip
M16.4	Bilateral post-traumatic osteoarthritis of hip
M16.50	Unilateral post-traumatic osteoarthritis, unspecified hip
M16.51	Unilateral post-traumatic osteoarthritis, right hip
M16.52	Unilateral post-traumatic osteoarthritis, left hip
M16.6	Other bilateral secondary osteoarthritis of hip
M16.7	Other unilateral secondary osteoarthritis of hip
M16.9	Osteoarthritis of hip, 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
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

ICD-10 Diagnosis Code	Description
M26.639	Articular disc disorder of temporomandibular joint, unspecified side
M26.69	Other specified disorders of temporomandibular joint

~~DESCRIPTION OF SERVICES~~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 non-prescription analgesics. HA gels have also been approved by the FDA for treatment of wrinkles and other facial contouring disorders. There is no evidene that use of one IA hyaluronan 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 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.

CLINICAL EVIDENCE

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Knee Osteoarthritis (OA)

A 2019 ECRI report on viscosupplementation 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 6ml 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 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 Gel-Syn (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 Gel-Syn (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).

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.

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.

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).

In a systematic review, Machado et al. (2013) analyzed the effectiveness of IA 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 IA 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 IA 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 IA injection of one given anti-inflammatory agent for each group. The control group was injected with saline solution into the IA space. The others were divided into 3 groups & received either HA (Hyalgan IA injection), betamethasone, or tenoxicam. Following the completion of injections, the changes in subjective symptoms were compared with VAS scores during 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 VAS, and modified Helkimo's clinical dysfunction index. 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 3 and 6 months ; 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

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 RClesions 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, but 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 February 25, 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 quality of life in patients with shoulder OA. However, additional studies are necessary.

Hip

Migliore et al. (2014) studied an innovative viscosupplement 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) 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 comorbilities. 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 years 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 comparing 2 monthly injections of IA bacterial-derived HA (Hyalubrix®) (HA) with local analgesia (mepivacaine). Outcomes were measured by the Lequesne algofunctional 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 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 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 Iinjection 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 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 (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, randomized controlled study, 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 quality of life (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 randomized controlled single-blind trial 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 postinjection 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 postinjection 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 randomized controlled trials (RCT) 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, 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 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. IA 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. IA injections were not addressed in recommendations for OA of the hand (Hochberg et al., 2012).

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).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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:

- 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
- Synojoynt: 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 February 25, 2019)~~

~~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 February 25, 2019)~~

~~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 February 25, 2019)~~

~~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 February 25, 2019)~~

~~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 February 25, 2019)~~

~~Gel-Syn™ (now known as Gelsyn-3) received FDA premarket approval on May 9, 2014. Additional information is available at the following websites:~~

- ~~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 February 25, 2019)~~

~~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 February 25, 2019)~~

~~Hymovis® received FDA approval on August 28, 2015. Additional information on is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p150010. (Accessed February 25, 2019)~~

~~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 February 25, 2019)~~

~~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 February 25, 2019)~~

~~TriVisc received FDA approval on November 13, 2017. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160057a.pdf. (Accessed February 25, 2019)~~

~~Synojoynt™ received FDA approval on May 8, 2018. Additional information is available at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm609709.htm. (Accessed February 25, 2019)~~

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. Local Coverage Determinations (LCDs) exist; see the LCDs for Hyaluronate Polymers, Hyaluronan Acid Therapies for Osteoarthritis of the Knee and Viscosupplementation Therapy for Knee.
(Accessed March 5, 2019)

REFERENCES

1. Altman RD, Rosen JE, Bloch DA, et al. Safety and efficacy of retreatment with a bioengineered hyaluronate for painful osteoarthritis of the knee: results of the open-label Extension Study of the FLEXX Trial. Osteoarthritis and Cartilage 2011; 19(10):1169-75.
2. American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guideline on the Treatment of Osteoarthritis of the Knee (Non-Arthroplasty). Rosemont (IL) Updated 2013.
3. Anika Therapeutics, Inc. Orthovisc high molecular weight hyaluronan. Package Insert. 530-220 AML 06/05. Woburn, MA: Anika Therapeutics; February 2006.
4. Bannuru RR, Natov NS, Dasi UR, et al. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. Osteoarthritis and Cartilage 2011; 19 (6): 611-9.
5. Bannuru RR, Natov NS, Obadan I, et al. Therapeutic Trajectory of Hyaluronic Acid Versus Corticosteroids in the Treatment of Knee Osteoarthritis: A Systematic Review and Meta-Analysis. Arthritis Rheum. 2009 Dec 15; 61(12):1704-11.
6. Brander VA, Gomberawalla A, Chambers M, et al. Efficacy and safety of hylan G-F 20 for symptomatic glenohumeral osteoarthritis: a prospective, pilot study. PM R. 2010 Apr; 2(4):259-67.
7. Chevalier X, Jerosch J, Goupille P, et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. Ann Rheum Dis. 2010 Jan; 69(1):113-9.
8. Chou WY, Ko JY, Wang FS, et al. Effect of sodium hyaluronate treatment on rotator cuff lesions without complete tears: a randomized, double-blind, placebo-controlled study. J Shoulder Elbow Surg. 2010 Jun; 19(4):557-63. Epub 2009 Dec 5.
9. DeGroot H, Uzunishvili S, Weir R, et al. Intra-articular injection of hyaluronic acid is not superior to saline solution injection for ankle arthritis: a randomized, double-blind, placebo-controlled study. Journal of Bone and Joint Surgery. American Volume 2012; 94(1):2-8.

10. Di Martino A, Di Matteo B, Papio T, et al. Platelet-Rich Plasma Versus Hyaluronic Acid Injections for the Treatment of Knee Osteoarthritis: Results at 5 Years of a Double-Blind, Randomized Controlled Trial. Am J Sports Med. 2018 Dec 13:363546518814532.
11. ECRI Institute. Viscosupplementation for Treating Osteoarthritic Knee Pain. Plymouth Meeting (PA): ECRI Institute; 2019 Jan 11. (Custom Rapid Responses).
12. Gencer ZK, Özkiriş M, Okur A, et al. A comparative study on the impact of intra-articular injections of hyaluronic acid, tenoxicam and betametazon on the relief of temporomandibular joint disorder complaints. JCraniomaxillofac Surg. 2014 Oct;42(7):1117-21.
13. Goiato MC, da Silva EV, de Medeiros RA, et al. Are intra-articular injections of hyaluronic acid effective for the treatment of temporomandibular disorders? A systematic review. Int J Oral Maxillofac Surg. 2016 Dec;45(12):1531-1537.
14. Gotxi-Erezuma I, Ortega-Galán M, Laso-Elguezabal A, et al. Electromyography-guided hyaluronic acid injection laryngoplasty in early stage of unilateral vocal fold paralysis. Acta Otorrinolaringol Esp. 2017 Sep - Oct;68(5):274-283.
15. Ha CW, Park YB, Choi CH, et al. Efficacy and safety of single injection of cross-linked sodium hyaluronate vs. three injections of high molecular weight sodium hyaluronate for osteoarthritis of the knee: a double-blind, randomized, multi-center, non-inferiority study. BMC Musculoskelet Disord. 2017 May 26;18(1):223.
16. Hayes, Inc. Hayes Health Technology Directory. Comparative Effectiveness Review of Hyaluronic Acid for Knee Osteoarthritis: A Review of Reviews. Lansdale, PA: Hayes, Inc.; October 31, 2017, updated November 2018.
17. Hochberg M, Altman R, Toupin-April K., et al. American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care & Research Vol. 64, No. 4, April 2012.
18. Juni, P, Reichenbach, S, Trelle, S, et al. Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: a randomized controlled trial. Arthritis Rheum. 2007; 56 (11):3610-3619.
19. Kwon YW, Eisenberg G, Zuckerman JD. Sodium hyaluronate for the treatment of chronic shoulder pain associated with glenohumeral osteoarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. J Shoulder Elbow Surg. 2013;22(5):584–594.
20. Lakhani R, Fishman JM, Bleach N, et al. Alternative injectable materials for vocal fold medialisation in unilateral vocal fold paralysis. Cochrane Database Syst Rev. 2012 Oct 17;10:CD009239.
21. Lau DP, Lee GA, Wong SM, et al. Injection laryngoplasty with hyaluronic acid for unilateral vocal cord paralysis. Randomized controlled trial comparing two different particle sizes. J Voice. 2010 Jan;24(1):113-8.
22. Long X, Chen G, Cheng AH, et al. A randomized controlled trial of superior and inferior temporomandibular joint space injection with hyaluronic acid in treatment of anterior disc displacement without reduction. J Oral Maxillofac Surg. 2009 Feb; 67(2):357-61.
23. Machado E, Bonotto D, Cunali PA. Intra-articular injections with corticosteroids and sodium hyaluronate for treating temporomandibular joint disorders: a systematic review. Dental Press J Orthod. 2013 Sep-Oct;18(5):128-33.
24. Majeed M. Relationship between serum hyaluronic acid level and disease activity in early rheumatoid arthritis. Ann Rheum Dis September 2004; 63(9): 1166-8.
25. Matsuno H, Yudoh K, Kondo M, et al. Biochemical effect of intra-articular injections of high molecular weight hyaluronate in rheumatoid arthritis patients. Inflamm Res. 1999; 48:154-159.
26. Mei-Dan O, Kish B, Shabat S, et al. Treatment of osteoarthritis of the ankle by intra-articular injections of hyaluronic acid: a prospective study. J Am Podiatr Med Assoc. 2010 Mar-Apr; 100(2):93-100.
27. Miaśkiewicz B, Szkiełkowska A, Piłka A, et al. Assessment of acoustic characteristics of voice in patients after injection laryngoplasty with hyaluronan. Otolaryngol Pol. 2016 Feb 29;70(1):15-23.
28. Migliore A, Massafra U, Bizzi E, et al. Duration of symptom relief after intra-articular injection of hyaluronic acid combined with sorbitol (anti-ox-vs) in symptomatic hip osteoarthritis. Int J Immunopathol Pharmacol. 2014 Apr-Jun;27(2):245-52.

29. Migliore A, Bizzi E, Massafra U, et al. The impact of treatment with hylan G-F 20 on progression to total hip arthroplasty in patients with symptomatic hip OA: a retrospective study. Curr Med Res Opin. 2012; 28(5):755-760.

30. Migliore A, Giovannangeli F, Bizzi E, et al. Viscosupplementation in the management of ankle osteoarthritis: a review. Archives of Orthopaedic and Trauma Surgery 2011; 131 (1):139-47.

31. Migliore A, Massafra U, Bizzi E, et al. Comparative, double-blind, controlled study of intra-articular hyaluronic acid (Hyalubrix) injections versus local anesthetic in osteoarthritis of the hip. Arthritis Res Ther. 2009; 11(6):R183. Epub 2009 Dec 9.

32. National Institute for Health and Care Excellence (NICE). Osteoarthritis. Care and management. 2014 Feb. 36 p. (Clinical guideline; no. 177).

33. Navarro-Sarabia F, Coronel P, Collantes E, et al. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Annals of the Rheumatic Diseases 2011;70(11):1957-62.

34. Newberry SJ, Fitzgerald JD, Maglione MA, et al. Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee. Technology Assessment Report. Prepared by RAND Southern California Evidence-Based Practice Center for the Agency for Healthcare Research and Quality (AHRQ). Project ID: DJDTO913. July 23, 2015.

35. Osti L, Buda M, Buono AD, et al. Clinical evidence in the treatment of rotator cuff tears with hyaluronic acid. Muscles Ligaments Tendons J. 2016 Feb 13;5(4):270-5.

36. Pavelka, K, Uebelhart, D. Efficacy evaluation of highly purified intra-articular hyaluronic acid (Sinovial®) vs hylan G-F20 (Synvisc®) in the treatment of symptomatic knee osteoarthritis. A double-blind, controlled, randomized, parallel-group non inferiority study. Osteoarthritis Cartilage. 2011;19(11):1294-1300.

37. Pei YC, Fang TJ, Hsin LJ, et al. Early hyaluronate injection improves quality of life but not neural recovery in unilateral vocal fold paralysis: an open-label randomized controlled study. Restor Neurol Neurosci. 2015;33(2):121-30.

38. Petrella RJ. Hyaluronic acid for the treatment of knee osteoarthritis: long-term outcomes from a naturalistic primary care experience. Am J Phys Med Rehabil. 2005 Apr;84(4):278-83; quiz 284, 293.

39. Richette P, Ravaud P, Conrozier T, et al. Effect of hyaluronic acid in symptomatic hip osteoarthritis: a multicenter, randomized, placebo-controlled trial. Arthritis Rheum. 2009 Mar;60(3):824-30.

40. Rutjes AW, Juni P, da Costa BR, et al. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Annals of Internal Medicine 2012;157(3):180-91.

41. Saito S, Furuya T, Kotake S. Therapeutic effects of hyaluronate injections in patients with chronic painful shoulder: a meta-analysis of randomized controlled trials. Arthritis Care & Research 2010; 62 (7):1009-18.

42. Saito S, Kotake S. Is there evidence in support of the use of intra-articular hyaluronate in treating rheumatoid arthritis of the knee? A meta-analysis of the published literature. Modern Rheumatology 2009;19 (5):493-501.

43. Salinas JB, Chhetri DK. Injection Laryngoplasty: Techniques and Choices of Fillers. Curr Otorhinolaryngol Rep (2014) 2: 131.

44. Samson DJ, Grant MD, Ratko TA,et al. Treatment of primary and secondary osteoarthritis of the knee. Evidence Report/Technology Assessment 2007; (157):1-157.

45. Sun SF, Hsu CW, Sun HP, et al. The effect of three weekly intra-articular injections of hyaluronate on pain, function, and balance in patients with unilateral ankle arthritis. Journal of Bone and Joint Surgery. American Volume 2011; 93 (18): 1720-6.

46. Tagliafico A, Serafini G, Sconfienza LM, et al. Ultrasound-guided viscosupplementation of subacromial space in elderly patients with cuff tear arthropathy using a high weight hyaluronic acid: prospective open-label non-randomized trial. European Radiology 2011; 21 (1): 182-7.

47. U.S. Department of Veterans Affairs; U.S. Department of Defense. VA/DoD Clinical Practice Guideline for the Non-Surgical Management of Hip & Knee Osteoarthritis. Version 1.0 – 2014.

48. Wang CC, Chang MH, Jiang RS, et al. Laryngeal electromyography-guided hyaluronic acid vocal fold injection for unilateral vocal fold paralysis: a prospective long-term follow-up outcome report. JAMA Otolaryngol Head Neck Surg. 2015 Mar;141(3):264-71.

49. Wang JY. Glycosaminoglycans are a potential cause of rheumatoid arthritis. Proc Natl Acad Sci U S A OCT-2002; 99(22): 14362-7.

50. Wang CC, Lee SH, Lin HY, et al. Short-term effect of ultrasound-guided low-molecular-weight hyaluronic acid injection on clinical outcomes and imaging changes in patients with rheumatoid arthritis of the ankle and foot joints. A randomized controlled pilot trial. Mod Rheumatol. 2017 Nov;27(6):973-980.

51. Witteveen AG, Hofstad CJ, Kerkhoffs GM. Hyaluronic acid and other conservative treatment options for osteoarthritis of the ankle. Cochrane Database Syst Rev. 2015 Oct 17;10:CD010643.

52. Witteveen AG, Sierevelt IN, Blankevoort L, et al. Intra-articular sodium hyaluronate injections in the osteoarthritic ankle joint: effects, safety and dose dependency. Foot and Ankle Surgery: Official Journal of the European Society of Foot and Ankle Surgeons 2010; 16 (4):159-63.

53. Zhang B, Thayaparan A, Horner N, et al. Outcomes of hyaluronic acid injections for glenohumeral osteoarthritis: a systematic review and meta-analysis. J Shoulder Elbow Surg. 2019 Mar;28(3):596-606.

54. 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 February 25, 2019)

55. 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 February 25, 2019)

56. 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 February 25, 2019)

57. 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 February 25, 2019)

58. 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)

59. 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 February 25, 2019)

60. Gel-Syn™ (now known as Gelsyn-3) received FDA premarket approval on May 9, 2014. Additional information is available at the following websites:

- **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 February 25, 2019)

61. 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 February 25, 2019)

62. Hymovis® received FDA approval on August 28, 2015. Additional information on is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p150010. (Accessed February 25, 2019)

63. 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 February 25, 2019)

64. 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 February 25, 2019)

65. TriVisc received FDA approval on November 13, 2017. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160057a.pdf. (Accessed February 25, 2019)

66. Synojoynt™ received FDA approval on May 8, 2018. Additional information is available at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm609709.htm. (Accessed February 25, 2019)

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
TBD	Template Update Changed policy type classification from "Medical Policy" to "Medical Benefit Drug Policy" Application Added language to indicate this policy does not apply to the states of Kansas and Louisiana; for the state of Louisiana, refer to the Medical Benefit Drug Policy titled *Sodium Hyaluronate (for Louisiana Only)* Removed language indicating this policy does not apply to the state of Tennessee *(state specific policy version no longer required)* Coverage Rationale Added language to clarify 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* Added language to indicate: Coverage for Durolane, Euflexxa, and Gelsyn-3 is contingent on criteria in the *Diagnosis-Specific Criteria* section of the policy; prior authorization is not required Coverage for GenVisc 850, Hyalgan, Supartz, Visco-3, Hymovis, Orthovisc, Synvisc or Synvisc-One, Gel-One, Monovisc, Triluron, TriVisc, or Synojoynt is contingent on the *Medical Necessity Criteria* and *Diagnosis-Specific Criteria* sections of the policy In order to continue coverage, members already on these products will be required to change therapy to Durolane, Euflexxa, or Gelsyn-3 unless they meet the *Medical Necessity Criteria* listed in the policy Treatment with GenVisc 850, Hyalgan, Supartz, Visco-3, Hymovis, Orthovisc, Synvisc or Synvisc-One, Gel-One, Monovisc, Triluron, TriVisc, or Synojoynt is medically necessary for the indications specified in this policy when one of the criteria below are met: Both of the following: History of a trial of adequate dose and duration of Durolane, Euflexxa, and Gelsyn-3, resulting in minimal clinical response Physician attests that, in their clinical opinion, the clinical response would be expected to be superior than experienced with Durolane, Euflexxa, and Gelsyn-3 or Both of the following: History of failure, contraindication, or intolerance to Durolane, Euflexxa, and Gelsyn-3 Physician attests that, in their clinical opinion, the same failure, contraindication, or intolerance would not be expected to occur with GenVisc 850, Hyalgan, Supartz, Visco-3, Hymovis, Orthovisc, Synvisc or Synvisc-One, Gel-One, Monovisc, Triluron, TriVisc, or Synojoynt Revised Diagnosis-Specific Criteria Applicable Codes

Date	Action/Description
	Updated list of applicable HCPCS codes to reflect quarterly code edits; added J7331 and J7332 Added ICD-10 diagnosis codes M16.0, M16.10, M16.11, M16.12, M16.2, M16.30, M16.31, M16.32, M16.4, M16.50, M16.51, M16.52, M16.6, M16.7, and M16.9 Supporting Information Updated *FDA* and *References* sections to reflect the most current information

INSTRUCTIONS FOR USE

This Medical **Benefit Drug** Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. 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.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The 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.