Policy Replaced with LCD L33432
Effective February 26, 2018

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Intra-articular Hyaluronan Injections for Osteoarthritis

Policy #: 084
Category: Medical

Latest Review Date: May 2017
Policy Grade: A

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

In accordance with Title XVIII of the Social Security Act, Section 1862 (a)(10) cosmetic surgery or expenses incurred in connection with such surgery is not covered except as required for the prompt repair of accidental injury or for improvement of the functioning of a malformed body member.

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Hyaluronan (HA) is a naturally occurring unbranched high-molecular weight polysaccharide distributed throughout the body, especially in connective tissues. It constitutes a major component of synovial fluid and of cartilage. This may contribute to the strong, elastic, and compressible nature of articular cartilage. When joint disease is present, changes are thought to occur in the quality and quantity of hyaluronan in the synovial fluid and cartilage. In osteoarthritis, there is a decrease in the overall length of the hyaluronan chains present in the cartilage and a decrease in the concentration of the hyaluronan in the synovial fluid. Intra-articular injections of hyaluronan or the derivative is a means of restoring the normal viscoelasticity of the synovial fluid in patients with osteoarthritis.

There is no curative therapy available for osteoarthritis and the goal is to reduce pain and prevent disability. Eight products have been approved by the FDA as an alternative to NSAID therapy for intra-articular injection in the treatment of osteoarthritis (OA) of the knee. They are Synvisc, Synvisc One, Hyalgan, Supartz, Orthovisc®, Euflexxa, Gel-One® and Monovisc™. All products are manufactured from rooster combs except Euflexxa, Orthovisc and Monovisc which are manufactured from bacterial fermentation. Synvisc and Euflexxa are injected intra-articularly into the knee joint once a week for three weeks, Orthovisc®, once a week for three to four weeks; Hyalgan and Supartz are injected intra-articularly once a week for five weeks; and Monovisc, for single dose treatment. Synvisc-One, Gel-One and Monovisc are all single-injection viscosupplementation products intended for use in the relief of pain associated with OA of the knee in those who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics.

Policy:

Effective for dates of service on or after September 4, 2010 and prior to February 26, 2018:

Blue Advantage will treat **intra-articular hyaluronan injections** as a **covered** benefit for osteoarthritis of the knee when **all** the following conditions are met:

- Conservative treatment has failed (at least **one** must have failed)
    - Physical therapy
    - Prior simple analgesic medication failure

Blue Advantage will treat **intra-articular hyaluronan injections** as a **non-covered** benefit and as **investigational** for any indication other than osteoarthritis of the knee.

Blue Advantage will treat **intra-articular hyaluronan injections** with **compounded** sodium hyaluronate as a **non-covered** benefit.

Retreatment is **covered after six months** if the prior treatment was effective.

Blue Advantage will treat **retreatment with Intra-articular hylan G-F 20 (Synvisc-One™)** as a **covered** benefit for retreatment every six months from the previous injection of Synvisc-One™ if improvement is documented or there is recurrence of significant pain. There is no data to support greater than 2 injections of Synvisc One™.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

This evidence review was originally created in July 1998 and has been updated regularly with searches of the MEDLINE database. The most recent literature review was performed through February 23, 2017.

Assessment of efficacy for a therapeutic intervention involves a determination of whether a technology improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, the placebo effect, and variable natural history of the condition. Because there are a number of RCTs on intra-articular (IA) hyaluronan for osteoarthritis (OA), this evidence review focuses on RCTs and systematic reviews.

Osteoarthritis is a degenerative joint disease that affects over 20 million people in the United States with over ten million being of the knee alone. Osteoarthritis occurs more in the weight bearing joints. It occurs more frequently in males before the age of 45 and after the age of 55 it is seen more in females. Osteoarthritis is second only to chronic heart disease as a leading cause of work disability. There is no known cure for osteoarthritis.

Knee Osteoarthritis

This evidence review was initially informed by a 1998 TEC Assessment on IA hyaluronan injections for OA, and incorporated material from a 2004 and a 2014 TEC Assessment and a 2007 TEC review for Agency for Healthcare Research and Quality (AHRQ). The 2007 AHRQ report concluded that results from 42 RCTs generally showed positive effects of viscosupplementation on pain and function scores compared with placebo for patients with primary OA of the knee. However, the evidence on viscosupplementation was accompanied by considerable uncertainty due to variable trial quality, potential publication bias, and unclear clinical significance of the changes reported. A 2016 protocol for an update of the 2007 AHRQ report does not IA hyaluronan because the technical expert panel concluded the evidence did not need updating.

The 2014 TEC Assessment involved a systematic review of recent meta-analyses on the treatment of knee OA with IA hyaluronan injections. Included in the evaluation were 5 meta-

analyses published between 2011 and 2013. Two meta-analyses concluded that IA hyaluronan provides a clinically meaningful benefit and 3 concluded that it did not, due to a lack of supportive evidence. It was not possible from the data to determine the proportions of patients achieving clinically meaningful improvement, although the analysis from the American Academy of Orthopaedic Surgeons (AAOS) determined that is was unlikely that an appreciable number of patients would benefit compared with placebo. It is also possible that the results supporting a clinically meaningful benefit were biased in favor of IA hyaluronan, due to unpublished trial data. When results from unpublished trials were obtained, the magnitude of treatment effect was notably lower compared with published results. Substantial heterogeneity between trials was also evident, increasing uncertainty. The TEC Assessment concluded that the 5 meta-analyses, sampling from a similar collection of published trials and 2 unpublished ones, highlight biases and difficulty ascertaining clinically meaningful patient-level improvements compared with placebo.

Literature reviews in 2016 and 2017 identified a number of additional systematic reviews and metaanalyses, published after the 2014 TEC Assessment. Some of these systematic reviews reported pooled analyses synthesizing results of RCTs that compared IA hyaluronan with placebo, and reported the outcome, pain. Three of the new meta-analyses concluded that IA hyaluronan injections for knee OA provided a clinically meaningful reduction in pain compared with placebo. One metaanalysis (Jevsevar et al [2015]) concluded that evidence from trials at low risk of bias (e.g., double-blind, sham-controlled) did not demonstrate a clinically meaningful benefit of IA hyaluronan. (Two of the metaanalyses concluding benefit of IA hyaluronan also limited analysis to trials at low risk of bias.) Two additional meta-analyses concluded that there was a small, statistically significant benefit and clinical significance depends on the threshold used. As noted in the 2014 TEC Assessment, "...for a standardized mean difference (SMD), a minimally important difference of -0.37 is sometimes cited…." The O'Hanlon (2016) meta-analysis of placebo-controlled, blinded trials found an SMD of -0.23. In contrast, the Johansen et al (2016) meta-analysis of placebo-controlled trials found an SMD of -0.39. However, when trials were stratified by risk of bias, the effect size of low-risk-of-bias trials was 0.0 and the effect sizes of the unclear and high-risk-of-bias trials were -0.81 and -0.35, respectively. Moreover, a stratified analysis by trial size found an SMD of -0.72, whereas trials with at least 100 patients showed an SMD of -0.21.

Conclusions that can be drawn from the newer meta-analyses are limited by potential biases with included trials. The presence of publication bias has been documented in the IA hyaluronan literature. Likewise, a small trial bias has been noted with effect estimates from smaller trials (<100 participants) almost 3-fold that of large trials. These observations are consistent with positive results from a small trial having a higher probability of being reported than a small negative one (or possibly a small negative trial having even been completed). In fact, the O'Hanlon (2016) meta-analysis did identify a small trial bias; although there was an overall positive impact of IA hyaluronan on pain, the effect size of small trials was much higher than that of large trials, and these effect size of large trials was below the level generally considered clinically significant. The results from the 2015-2016 meta-analyses (which did not include any new placebo-controlled randomized trials) do not alter conclusions of the 2014 TEC Assessment on the impact of IA hyaluronan on health outcomes in patients with knee OA.

In conclusion, this analysis demonstrated that intra-articular injection of US-approved HA products were both safe and efficacious in patients with symptomatic knee osteoarthritis.

Hip Osteoarthritis

A 2015 systematic review by Lieberman et al included RCTs and observational studies (with a minimum of 10 patients) evaluating IA hyaluronan for treatment of pain associated with hip OA.28 Twenty-three studies were identified, 6 of which were RCTs. The studies evaluated 11 different formulations of IA hyaluronan. Durations of follow-up varied; 19 studies followed patients for 6 months or less, 3 studies had between 6 months and 1 year of follow-up, and 1 study followed patients for more than 1 year. The primary efficacy outcome was change from baseline in pain measured by a VAS. Reviewers did not report the number of points on the VAS, but presumably this differed across studies and the authors appeared to standardize results on a 10-point VAS. A pooled analysis of data from all studies found a statistically significantly lower pain score at follow-up compared to baseline. Mean change was -1.97 points on the VAS (95% CI, -2.83 to -1.12). In a pooled analysis of the 6 RCTs, there was a significantly greater decrease in pain with IA hyaluronan than with a control intervention (-0.27 points on a VAS; 95% CI, -0.43 to -0.11). Although statistically significant, a between-group difference of 0.27 points on a VAS may not be clinically meaningful.

In 2016, Piccirilli et al published a systematic review of RCTs evaluating IA hyaluronan for any type of hip disorder. They identified 25 RCTs; the trials addressed hip OA, hip rheumatoid arthritis, and femoroacetabular impingement. Reviewers provided a table of individual studies and noted that studies used different modalities and protocols; no attempt was made to synthesize findings quantitatively or qualitatively.

Ankle Osteoarthritis

The evidence was examined from published RCTs and systematic reviews. A 2015 Cochrane review by Witteveen et al addressed IA hyaluronan and other conservative treatments for ankle OA. Reviewers identified 6 RCTs, 3 of which were double-blind and compared IA hyaluronan with placebo. The other trials were single-blind. Two of them compared IA hyaluronan to another treatment (exercise in 1 study, botulinum toxin in the other) and the sixth trial compared different doses of hyaluronan. Five of the 6 trials included patients with unilateral ankle pain. Sample sizes at randomization ranged from 17 to 75, and length of follow-up ranged from 3 to 12 months. The authors pooled findings only for 2 of the 3 studies comparing IA hyaluronan and placebo. Meta-analyses of efficacy outcomes (pain, function) did not find statistically significant benefit favoring IA hyaluronan over placebo, with the exception of the outcome Ankle Osteoarthritis Scale (AOS) total score at 6 months. For the AOS outcome, the pooled effect size was -12.53 (95% confidence interval [CI], -23.84 to -1.22) in favor of IA hyaluronan; however, the evidence for this analysis was rated as low due to the limitation in study design (ie, unclear risk of bias) and "…imprecision of result (low number of participants)." No serious adverse events were reported and no patient withdrew from the trial due to an adverse event.

A 2011 review of IA hyaluronan for ankle OA by Migliore et al considered RCTs and observational studies. They identified 3 small RCTs with a total of 75 patients, and 4 case series. In 2 of the RCTs, IA hyaluronan was compared with placebo injection and the third RCT

compared IA hyaluronan with exercise therapy. Reviewers were unable to conduct a meta-analysis due to the limited number of studies and study heterogeneity.

Foot Osteoarthritis
There is a very limited amount of evidence on IAHA injections in the foot. Munteanu et al reported on an RCT of a single IAHA injection in 151 patients with first metatarsophalangeal joint OA. At one, three, and six months' follow-up, there were no significant differences between the IAHA and placebo groups on the Foot Health Status Questionnaire.

Thumb Osteoarthritis
Two systematic reviews have evaluated IA hyaluronan and corticosteroid injections for treating thumb OA. The 2016 review by Kroon et al identified 3 studies comparing IA hyaluronan and placebo and 6 comparing IA hyaluronan and corticosteroids. Findings from the IA hyaluronan studies were not pooled. Unlike the Kroon review, the 2015 systematic review by Trellu et al included only RCTs and pooled study data. Six trials (total N=428 patients) were included in the meta-analyses; 169 patients were treated with HA, 147 with corticosteroids, and 74 with placebo. In pooled analyses of trails comparing IA hyaluronan and placebo (74 patients in each arm), there was no significant between-group difference in pain at week 12 (standardized response mean [SRM], -0.95; 95% CI, -3.87 to 1.97); however, functional capacity at week 12 was significantly better after IA hyaluronan than after placebo (SRM = -1.14; 95% CI, -1.69 to -0.60). When IA hyaluronan and corticosteroids were compared, there were no significant differences in pain, functional capacity, or pulp pinch force at 12 weeks. At 24 weeks, findings were mixed. There was no significant between IA hyaluronan and corticosteroids in functional capacity, IA hyaluronan was superior on pulp pinch force status (SRM = -1.66; 95% CI, -0.75 to -2.57), and corticosteroids were superior on pain (SRM=1.44; 95% CI, 0.14 to 2.74).

Shoulder Osteoarthritis
A 2014 systematic review by Colen et al identified RCTs, controlled observational studies, and case series evaluating IA hyaluronan for treatment of glenohumeral OA in adults. Eight studies met the eligibility criteria; 2 were RCTs, 5 were prospective case series, and 1 was a retrospective case- control study. Due to heterogeneity across studies and the small number of controlled studies, reviewers did not pool study findings on the efficacy of IA hyaluronan compared with placebo or an alternative intervention for treating shoulder OA. The RCTs are described next.

In 2013, Kwon et al reported a multicenter randomized double-blind placebo-controlled trial of IAHA in 300 patients with glenohumeral OA. Intent-to-treat analysis found similar improvement in VAS for pain (19.88 mm for IAHA and 16.29 mm for placebo) and in the Outcome Measures in Rheumatoid Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) high responder rate (40.8% for IAHA and 34.9% for sham). In a subset of patients there was a statistically significant difference in VAS of 4.0 mm on a 100 mm scale and 8.37% on the OMERACT-OARSI. However, the clinical significance of these differences is uncertain.

The evidence on the efficacy of IAHA for joints other than the knee is less robust. While some studies show benefit, others do not, and systematic reviews have not concluded that there is a

clinically significant benefit. This evidence is not sufficient to conclude that IAHA treatment of joints other than the knee improves outcomes.

An industry-sponsored RCT of 660 patients with persistent shoulder pain due to glenohumeral joint OA, rotator cuff tear, and/or adhesive capsulitis compared three weekly injections versus five weekly injections of sodium hyaluronate (Hyalgan) versus five weekly injections of saline. Approximately 60% of patients had OA, although the majority of those with OA also had rotator cuff disorders or capsulitis. Sixty-nine percent (n=456) of the patients had a follow-up visit at 26 weeks. There was no significant difference among groups in the primary outcome measure, shoulder pain with movement at 13 weeks. Analysis of predefined, stratified subgroups revealed no significant differences in reported pain at 13 weeks but a significant decrease in reported pain in both treatment groups at 26 weeks compared to placebo among patients with OA. In those without OA, there was no significant improvement with either regimen. Of note, this appears to be an as-treated analysis of the OA subgroup data. Differences in range of motion among groups were judged to be not clinically important.

A meta-analysis of 19 blinded RCTs published between 1988 and 2008 examined the use of IAHA for chronic painful shoulder in a total of 2,120 patients. A variety of shoulder disorders were included, e.g., adhesive capsulitis, rotator cuff tear, shoulder impingement syndrome, and frozen shoulder. Sample size ranged from 20 to 660 patients, mean trial duration was 3.5 weeks, and mean Jadad score was 3.5 ± 1.5. Ten trials (1,435 patients) reported pain outcomes. The combined effect size (standardized mean difference) for categorical and continuous pain ratings favored IAHA (0.39, (95% CI: 0.26, 0.53)). There was no heterogeneity and no evidence of publication bias. Because the studies included in the meta-analysis were of short duration and included a variety of shoulder diseases, they do not provide conclusive evidence of the effectiveness of IAHA in OA of the shoulder.

Spine Osteoarthritis
The data are limited to small pilot studies and case series.

Other
Data from small pilot studies, and case series have been reported using hyaluronan for arthritis of the spine and for lateral condylitis of the elbow (tennis elbow).

Summary
Intra-articular injection of hyaluronan (IAHA) into osteoarthritic joints is thought to replace hyaluronan, restore the viscoelastic properties of the synovial fluid, and improve pain and function. The largest amount of evidence is on treatment of OA of the knee. Individual trials show inconsistent results in pain and functional outcomes for IAHA compared to placebo or active control. Meta-analyses of RCTs, however, support the clinical effectiveness of IAHA in OA of the knee. In general, studies report that IAHA had later onset but longer duration of action compared to intra-articular corticosteroid injections. A recent RCT found repeated injections of IAHA progressively increased the number of patients responding to IAHA. A positive carry-over effect for up to one year was also noted after repeated injections of IAHA. Therefore, based on a compilation of available evidence, IAHA injections for osteoarthritis of the knee appear to reduce pain and improve health outcomes and may be considered medically necessary.

IAHA continues to be investigated for off-label uses in other joints. Current evidence on these off-label uses is limited, consisting of small RCTs and case series. Some RCTs on IAHA injections for OA of the ankle, foot, hand and shoulder have shown treatment benefits; however, these studies are not consistent in reporting improvements that are significantly greater than placebo and/or control treatments. RCTs on IAHA injections for OA of the hip have also been inconsistent, with some RCTs reporting improvements in outcomes with IAHA hip injections and others reporting no improvement. Currently, given the limited and inconsistent available data, these uses are considered investigational.

Practice Guidelines and Position Statements

In 1995, the American College of Rheumatology (ACR) published guidelines for the treatment of osteoarthritis (OA) of the knee, which recommended acetaminophen as first-line therapy, followed by low-dose ibuprofen, and then full-dose nonsteroidal anti-inflammatory drugs (NSAIDs), when necessary. In 2000, the ACR published updated guidelines on the management of hip and knee OA. These guidelines recommend nonpharmacologic approaches and drug therapy for management of hip and knee OA. Intra-articular hyaluronan or glucocorticoids are considered alternative approaches to oral agents for knee OA based on studies demonstrating effectiveness in reducing knee pain. However, the guidelines note there aren't any studies demonstrating the efficacy of intra-articular hyaluronan or glucocorticoids for hip OA. Updated guidelines from 2012 addressed OA of the hand, hip, and knee. A conditional recommendation was given for IAHA to treat OA of the knee. The ACR recommends not using IAHA for OA of the hand. For OA of the hip, the ACR explicitly makes no recommendation regarding treatment with IAHA.

The Osteoarthritis Research Society International (OARSI) guidelines, developed by consensus after review of existing guidelines and systematic reviews, recommend:

> "Injections of IA [intra-articular] hyaluronate may be useful in patients with knee or hip OA [osteoarthritis]. They are characterized by delayed onset, but prolonged duration, of symptomatic benefit when compared to IA injections of corticosteroids."

The recommendation is made with a strength of 64%, CI 43–85%.

The 2009 Bannuru et al meta-analysis, noted above, was cited in a 2010 evidence update by OARSI. In an accompanying editorial, OARSI authors note that IAHA "has a time-dependent trajectory of therapeutic effect. Thus, the time point at which its outcome is assessed will influence its apparent effectiveness."

The American Academy of Orthopaedic Surgeons' (AAOS) 2008 guideline on the non-arthroplasty treatment of OA of the knee indicates a recommendation cannot be made for IAHA for mild to moderate symptomatic knee OA. The guideline notes available evidence is inconclusive. However, this AAOS guideline does indicate intra-articular corticosteroid injections are suggested for short-term pain relief for symptomatic knee OA based on fair evidence.

The 2009 AAOS Clinical Practice Guideline on glenohumeral joint osteoarthritis includes a weak Grade C recommendation that "the use of injectable viscosupplementation is an option when treating patients with glenohumeral [shoulder] osteoarthritis." Grade C recommendations are based on poor-quality evidence. In this instance, the recommendation is based on a single case series of 30 patients with OA of the glenohumeral joint who received three weekly IA injections of Synvisc. At one, three, and six months, clinically significant improvements were seen in pain, function, and quality of life measures.

Guidelines published by the National Institute for Health and Clinical Excellence (NICE) do not recommend IAHA injections for the treatment of OA because "the cost-effectiveness estimate is outside the realms of affordability" to the National Health Service. However, guideline developers state, "Overall, the evidence suggests that hyaluronan and hylan derivatives seem to be superior to placebo in terms of efficacy and quality of life outcomes in patients with OA in the knee at different post-injection periods but especially at the five- to 13-week post-injection period." Toxicity of IAHA was noted to be small.

The American Academy of Orthopaedic Surgeons (AAOS) updated their Clinical Practice Guideline for Treatment of Osteoarthritis of the Knee in 2013. In their recommendations, the AAOS states that they "cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee." It was noted that the recommendation was based on lack of efficacy, not on potential harm.

Key Words:

Intra-articular injection, Hyalgan, Synvisc, Supartz, Hylan G-F 20, osteoarthritis, hyaluronic acid, Orthovisc®, high molecular weight hyaluronan, Euflexxa™, Synvisc-One™, Gel-One®, Monovisc™, Gel-Syn™, GenVisc 850™

Approved by Governing Bodies:

Several preparations of intra-articular (IA) hyaluronan have been approved by the U.S. Food and Drug Administration (FDA) as an alternative to nonsteroidal anti-inflammatory drug therapy in the treatment of osteoarthritis (OA) of the knee: Synvisc® and Synvisc-One® (Genzyme); Gel-One® (Zimmer); Hyalgan® (Fidia); Supartz FX™ (Bioventus); Orthovisc® (Anika); Euflexxa®, previously named Nuflexxa (Savient); Monovisc® (Anika Therapeutics); and Gel Syn™ (Institut Biochimique SA). All products are manufactured from rooster combs, except for Euflexxa®, Orthovisc®, Monovisc®, Gel-Syn™, and GenVisc 850, which are produced from bacterial fermentation. Also, Synvisc® undergoes additional chemical crosslinking to create hylans with increased molecular weight (6000 kDa) compared with Hyalgan® (500-730 kDa) and Supartz™ (620-1170 kDa). Monovisc® is also cross-linked with a proprietary cross-linker. The differing molecular weights of the products lead to different half-lives; the half-life of Hyalgan® or Supartz™ is estimated at 24 hours, while the half-life of Synvisc® may range up to several days.

According to manufacturers' prescribing information for Synvisc® and Euflexxa®, IA hyaluronan is "indicated for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy, and to simple analgesics, eg, acetaminophen." The product inserts further indicate that Synvisc® and Euflexxa® should be injected intra-articularly into the knee joint once per week for a total of 3 injections over a 2- to 3-week period. In contrast, 5 weekly injections are recommended for the Hyalgan® and Supartz™ products, and 3 to 4 weekly injections are recommended for Orthovisc®. In February 2009, FDA approved the use of single-dose hylan G-F 20 (Synvisc-One®) for the treatment of OA of the knee. In 2011, FDA approved the use of the single-dose cross-linked hyaluronate Gel-One® (also known as Gel-200) for the treatment of OA of the knee. In 2014, Monovisc® was also approved as a single-dose treatment, while Gel-Syn™ was approved as a course of 3 weekly injections. In 2015, GenVisc 850 was approved as a course of 3 weekly injections.

In 2000, FDA approved removal of a precautionary statement from the package inserts for Hyalgan® and Synvisc®, which indicated that stated that the safety and efficacy of repeat courses had not been established.
FDA has not approved intra-articular hyaluronan for joints other than the knee.

FDA product code: MOZ.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT codes:

Monovisc™ coding - There is currently not a code for Monovisc™

Use:

J3490	Unclassified drugs **(Effective February 25, 2014)**
J7320	Hyaluronan or derivative, GenVisc 850, for intra-articular injection, 1 mg **(Effective January 1, 2017)**
J7321	Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose **(Effective January 1, 2008)**
J7322	Hyaluronan or derivative, Hymovis, for intra-articular injection, 1 mg. **(Effective January 1, 2017)**
J7323	Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose **(Effective January 1, 2008)**
J7324	Hyaluronan or derivative, Orthovisc, for intra-articular injection, per dose **(Effective January 1, 2008)**
J7325	Hyaluronan or derivative, Synvisc or Synvisc-one, for intra-articular injection, 1 mg **(Effective January 1, 2010)**
J7326	Hyaluronan or derivative, Gel One, for intra-articular injection, per dose **(Effective January 1, 2012)**

J7327 Hyaluronan or derivative, Monovisc, for intra-articular injection, per dose **(Effective January 1, 2015)**

J7328 Hyaluronan or derivative, gel-syn, for intra-articular injection, 0.1 mg **(Effective January 1, 2016)**

Previous Coding:

Synvisc-One™ coding - There is currently not a code for Synvisc ™

J3490 Unclassified drugs **(Effective February 26, 2009 through December 31, 2009)**

J7322 Hyaluronan or derivative, Synvisc, for intra-articular injection, per dose **(Code deleted effective January 1, 2010)**

Q9980 Hyaluronan or derivative, genvisc 850, for intra-articular injection, 1 mg**(Code deleted effective December 31, 2016)**

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