Name of Policy:
Intra-articular Hyaluronan Injections for Osteoarthritis

Policy #: 084
Category: Medical

Latest Review Date: February 2014
Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
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. Synvise 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. Synvise-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:
All intra-articular hyaluronan injections meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for osteoarthritis of the knee when the following condition is met:

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

Intra-articular hyaluronan injections do not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational for any indication other than osteoarthritis of the knee.

Intra-articular hyaluronan injections with compounded sodium hyaluronate do not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage.

Retreatment is covered after six months if the prior treatment was effective.
Effective for dates of service on February 26, 2009 through September 3, 2010:

**Intra-articular hylan G-F 20 (Synvisc-One™) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for treatment of osteoarthritis of the knee when the following criteria is met:

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

**Retreatment with Intra-articular hylan G-F 20 (Synvisc-One™) meets** Blue Cross and Blue Shield of Alabama’s medical criteria 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 two injections of Synvisc One™.

*Blue Cross and Blue Shield of Alabama 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 Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate 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:**

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.

In 1995, the American College of Rheumatology presented guidelines for the medical management of osteoarthritis of the knee. The presence of comorbid conditions should be taken into consideration when treating patients. Nonpharmacologic therapies include professional social support, weight loss if overweight, physical therapy, occupational therapy, and aerobic exercise programs. Pharmacologic therapy includes intra-articular steroid injections, non-opioid analgesics, topical analgesics, nonsteroidal antiinflammatory drugs and opioid analgesics. The U.S. Food and Drug Administration, as an alternative to NSAID therapy in the treatment of osteoarthritis of the knee, has approved three preparations of intra-articular hyaluronan.

Based on the 1998 TEC assessment, a number of randomized controlled trials comparing intra-articular hyaluronan to placebo were reviewed. The evidence was determined as being consistent in suggesting that a small incremental benefit is associated with intra-articular hyaluronan treatment over the benefit achieved with placebo-control treatments. In 2000, the FDA approved revised labeling for Hyalgan regarding repeat treatment cycles by deleting the statement that “safety and effectiveness of repeat treatment cycle (of Hyalgan and Synvisc) have not been established”. The Hyalgan manufacturer stresses that there are “no safety restrictions on retreatment when patients require additional relief.” A literature review of safety and efficacy...
for multiple courses of viscosupplementation indicate no loss in efficacy for repeat courses. Pseudoseptic reactions were more frequently reported with hylan G-F 20 than with sodium hyaluronate. No changes for Synvisc have been made in labeling.

Intra-articular hyaluronan is only recommended for use in the treatment of osteoarthritis of the knee. No other joint has been approved for use.

Some pharmacies have compounded sodium hyaluronate for injection. These drugs are not regulated to ensure the ingredient percents or sterility, therefore, are not recommended as the drug of choice for injection.

In 2005, a Cochrane review of viscosupplementation for OA of the knee was published that evaluated a total of 63 clinical trials identified from a literature review conducted up to April 2004. Overall, the review concluded hyaluronan is safe and effective in improving joint pain and function and global patient function in the treatment of OA of the knee. Included in the 63 trials evaluated for the review were 37 trials comparing hyaluronan/hylan products to placebo. The pooled analyses for these 37 trials demonstrated that hyaluronan treatment was more effective than placebo, most notably in the five to 13 weeks after treatment. Five trials were evaluated that compared hyaluronan (HA) to NSAIDs. In the analysis of this comparison, HA was found to be comparable in efficacy to NSAIDs. In nine trials comparing HA to corticosteroid injections, analysis demonstrated longer term benefits with HA than with corticosteroid injections. The authors noted that the clinical effects of the HA products have considerable heterogeneity and therapeutic variability. However, conclusions about the clinical effectiveness of products could not be drawn given the limited data comparing products head-to-head.

Another 2005 systematic review and meta-analysis by Arrich et al evaluated 22 randomized controlled trials (RCTs) through April 2004 on hyaluronic acid injections for OA of the knee. The authors’ analysis found pain relief from OA of the knee related to movement was only slightly better with hyaluronic acid injections than placebo but was of borderline clinical significance. Also, pain at rest and joint function were not improved with hyaluronic acid injections. The authors emphasized the poor methodologic quality of the trials and thereby concluded that there was no proof that hyaluronic acid injections provide clinically relevant benefits, and they may even increase the incidence of adverse events.

The conclusions of the Cochrane review are consistent with the 2004 TEC Special Report. While hyaluronan has some beneficial effect, the magnitude and clinical significance of the effect may be small. As noted in the Cochrane review, further research would be useful, such as head-to-head comparisons of the various HA products, longer term trials (up to one year), and trials examining repeated courses of treatment with HA. The Arrich et al review also found improvement in pain with hyaluronic acid injections but emphasized that the benefits were borderline in clinical significance. However, the Arrich trial reviewers concluded that the evidence was not sufficient to demonstrate the clinical effectiveness of hyaluronic acid injections. Therefore, the authors recommended hyaluronic acid injections not be used for the treatment of pain in OA of the knee until large clinical trials determine the clinical benefits on defined clinical endpoints versus the risk of adverse events.
An April 2006 update of the Cochrane review of viscosupplementation for OA of the knee evaluated a total of 76 clinical trials identified from a literature review conducted up through the first week of January 2006. The Cochrane review came to the same conclusions it had made previously, as noted earlier, including that HA treatment was more effective than placebo, most notably in the five to 13 weeks after treatment. In a meta-analysis of literature reviewed in a search conducted through October 2004, Pagnano and Westrich concluded that repeat courses of HA for OA of the knee were as safe and effective as a single course of HA injections. Pseudoseptic reactions were more frequently reported with hylan G-F 20 (Synvisc) than with sodium hyaluronate (Hyalgan, Supartz, Euflexxa). However, as noted in the 2004 TEC Special Report, there is no rigorous controlled evidence regarding the effectiveness of repeated treatments with HA.

In 2007, the TEC Evidence-based Practice Center published a technology assessment for the Agency for Healthcare Research and Quality (AHRQ) on the treatment of primary and secondary OA of the knee.

The report concluded that:
- Results from 42 trials (n=5,843) generally show positive effects of viscosupplementation on pain and function scores compared to placebo for patients with primary OA of the knee. However, the evidence on viscosupplementation is accompanied by considerable uncertainty due to variable trial quality, potential publication bias, and unclear clinical significance of the changes reported.
- Trials of hylan G-F 20 (Synvisc, 6,000 kDa), the highest molecular weight cross-linked product, generally reported better results than other trials.
- There was no evidence for differential effects according to subgroups defined by age, sex, primary/disease, BMI [body mass index]/weight, or disease severity.
- Minor adverse events accompanying intra-articular injections are common, but the relative risk accompanying hyaluronan injections over placebo appears to be small. The risk of local adverse events appears to increase with prior courses of treatment. Pseudoseptic reactions associated with hyaluronan appear relatively uncommon but can be severe.

**March 2009 Update**

**Knee**

In the clinical trial for Synvisc-One a total of 253 patients in 21 sites in six countries were treated in the prospective, well-controlled, randomized double-blind, two-arm study. Outcome measures collected were based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), patient global assessment (PTGA), clinical observer global assessment (COGA) and use of rescue analgesic. Primary efficacy analysis was a comparison over 26 weeks between the two treatment groups of change from baseline in the WOMAC A (Pain) Subscale. Study patients were at least 40 years old and had primary osteoarthritis of the knee. Patients were followed for 26 weeks with multiple, scheduled follow-up visits from the date of treatment. Synvisc-One demonstrated statistically significant superiority to placebo injection in multiple pre-defined secondary outcome measures. These included PTGA over 26 weeks, PTGA at 26 weeks, COGA over 26 weeks, COGA at 26 weeks, and pain while walking on a flat surface both over 26 weeks and at 26 weeks. The conclusions demonstrated a statistically significant estimated treatment
difference between the two treatment groups. The study showed that patients receiving Synvisc-One had significantly less pain over six months, and felt significantly better that those receiving the placebo. Overall, the study confirmed a favorable risk/benefit profile of a single injection of 6 ml of Synvisc in patients with symptomatic primary OA of the knee. The repeat treatment phase confirmed the safety profile of the initial phase with no increase of adverse events in patients receiving a second injection of Synvise-One a 26 weeks. Safety and efficacy has not been established in pregnant women and in children.

**Hip**
There are a number of small RCTs and systematic reviews that evaluate IAHA for OA of the hip. The largest RCT randomized 101 patients to receive either HA injections or saline. There was a small reduction in pain with walking in patients treated with HA injections over the three-month evaluation period, whereas patients injected with corticosteroid had larger and significant pain reductions with walking. Two systematic reviews identified this study, which did not show significant benefit of viscosupplementation over placebo, and one RCT comparing hyaluronan of different molecular weights. Although the case series reviewed in these papers suggested that HA “might have a beneficial effect in relieving pain” in patients with hip osteoarthritis, in the absence of comparative studies, efficacy could not be evaluated.

A 2008 systematic review of two RCTs and nine cohort studies concluded that viscosupplementation therapy with HA appears to be “a safe and effective method in the treatment of hip OA resistant to conventional treatment modalities.” However, the authors recommend future studies with a large number of patients to confirm results and to answer questions about doses, intervals between doses, and the number of injections needed to achieve a therapeutic and safe effect.

A study to evaluate the efficacy and tolerability of a single intraarticular (IA) injection of hyaluronic acid (HA) for the treatment of hip osteoarthritis was published in March 2009 by Richette et al. This was a multicenter, randomized; parallel-group placebo-controlled trial was conducted over three months. Participants were from age 30 to 80 and met the criteria for the diagnosis of hip OA. Patients were randomized to receive either HA or a placebo of saline. Fluoroscopy was used for guidance in a deep joint such as the hip. Eighty-five patients were randomized to either group. At three months, the decrease in pain score did not differ between the HA and placebo group which was the primary endpoint. Other secondary endpoint measures also did not differ between the groups. Prior to this study data was scarce regarding injections into the hip for OA. The authors report that to their knowledge, the first RCT to evaluate the efficacy of a single injection of HA for the treatment of hip OA. This study was based on a single injection for treatment, which per the authors might have been insufficient to have an effect of OA symptoms. The authors believe that future studies are warranted to confirm results of this study and to evaluate effects of repeated injections in hip OA.

**April 2009 Update**
The Agency for Healthcare Research and Quality (AHRQ) has issued a guide for clinicians that summarizes the evidence on the effectiveness and safety of three treatments for osteoarthritis of the knee. The information included in this guide regarding viscosupplementation with hyaluronan is of interest to this policy. In patients with OA of the knee, published clinical trials
comparing injections of visco-supplements with placebo have yielded inconsistent results. Higher quality and larger trials have generally found lower levels of clinical improvement in pain and function than small and poor quality trials. Any clinical improvement attributable to viscosupplementation is likely small and not clinically meaningful. Overall, evidence is insufficient to demonstrate clinical benefit for the higher molecular weight products.

December 2011 Update

Gel-One® is a hyaluronate hydrogel, recently FDA approved on March 22, 2011, used to relieve knee pain due to osteoarthritis in patients who have not been able to get enough relief from NSAIDS or simple pain medications or from exercise and physical therapy. Gel-One® is designed as a single injection treatment to reduce pain associated with osteoarthritis of the knee for up to 13 weeks. The safety and effectiveness of a single injection of Gel-One® for the treatment of symptomatic osteoarthritis of the knee were studied in a prospective, randomized and double-blind controlled study conducted at 25 centers in the U.S. A total of 377 patients received treatments, 249 patients were injected Gel-One® and 128 patients were injected saline control. Patients were asked to rate their pain during five conditions of activity or rest: how much pain during walking on a flat surface, during going up or down stairs, at night in bed, during sitting or lying down, and during standing. Patients rated their pain from 0 to 100 (bad pain) by marking on a 100 mm line. Pain was evaluated in this manner at 1, 3, 6, 9, and 13 weeks after injection. The pain scores were used to compare the effectiveness of Gel-One® injection to saline control injection. Patients receiving Gel-One® experienced more improvement in knee pain over 13 weeks than patients who received saline control injections. The pain score was reduced by an average of 39.3% and average pain score reduction of 27.8 mm (on the 100mm pain scale) from the baseline score in patients receiving Gel-One® , whereas the pain score was reduced by an average of 33.2% with an average pain score reduction of 22.6 mm in patients receiving saline as a control. The safety and effectiveness of Gel-One® have not been established in pregnant women or in pediatric patients (≤21 years of age).

January 2012 Update

Knee

In 2009, Bannuru et al conducted a meta-analysis of seven RCTs published between 1987 and 2004 that compared pain relief achieved with IAHA or intra-articular (IA) corticosteroids in 610 patients with OA of the knee. Trial quality was fair, heterogeneity was moderate (I², 37-49% at various time points), and publication bias was suggested by an asymmetric funnel plot and positive Egger test. At week two, the effect size favored corticosteroids (0.39 [95% confidence interval (CI): -0.65, -0.12]); at week four, the effect size suggested equal efficacy (-0.01 [95% CI: -0.23, 0.21]); and at week eight, there was a non-significant effect size favoring IAHA (0.22 [95% CI: -0.05, 0.49]). At weeks 12 and 26, statistically significant effect sizes favoring IAHA were found (0.35 [95% CI: 0.03, 0.66], and 0.39 [95% CI: 0.18, 0.59], respectively).

Bannuru et al published another meta-analysis of IAHA for knee OA in 2011. This meta-analysis evaluated 54 randomized clinical trials published between 1983 and 2009, 49 of which compared the effects over time of IAHA to placebo for pain relief in a total of 6,962 patients. Trial quality and conduct varied. By week four, the effect size favored IAHA (0.31; 95% CI 0.17, 0.45), peaked at eight weeks (0.46; 95% CI 0.28, 0.65), and decreased by week 24 to a lesser residual effect (0.21; 95% CI 0.10, 0.31). The authors noted the therapeutic effect was also consistent on
multivariate analysis of the subset of high quality trials (2,570 participants) adjusting for correlation between time points.

A multi-center, placebo-controlled, double-blind RCT administered five weekly Hyalgan or saline placebo IA injections to 335 patients with OA of the knee (335 knees) and assessed survival of response at three, six, nine, and 12 months. Survival of response was defined using the Lequesne algofunctional index (LFI), an international index for scoring pain and function in OA using a 0-24 point scale. The LFI is a modification of the WOMAC Index of Osteoarthritis, a 24-item self-administered questionnaire that assesses pain, stiffness, and function in OA patients. The LFI is not as well-validated as the WOMAC. In this study, a one-point decrease in LFI score defined the onset of improvement, and a one-point increase in LFI score defined recurrence. These changes may not be clinically relevant. There was no statistically significant difference between groups in the time to recurrence (Hyalgan group, 172 days; placebo group, 204 days, p=0.26). The total number of adverse events in the Hyalgan and placebo groups was 133 and 178, respectively. Local injection site pain, joint pain exacerbation, and “infections in general” were reported more often in the placebo group.

In a double-blind, placebo-controlled RCT from investigators in Turkey, 45 patients with OA of the knee (48 knees) were randomly assigned to receive two weekly IA injections of Orthovisc or saline placebo. At one, three, five, and 14 weeks, there was no difference in visual analog scale (VAS) for pain or in overall WOMAC Index.

Results from an RCT on the effects of repeat IAHA for knee OA (the AMELIA project) were published in 2011. In this trial of 306 patients, five injections of IAHA or placebo were given weekly for four treatment cycles. Patients were followed a total of 40 months, including a six-month follow-up after the first and second cycles and a one-year follow-up after the third and fourth cycles. Patients were not permitted to use non-steroidal anti-inflammatory medications one week before follow-up evaluations, nor were they permitted to receive corticosteroid injections in the treatment knee during the entire study period. After each treatment cycle, more patients in the IAHA group progressively responded (from 71.1% to 80.5%) compared to the placebo group (from 67.8% to 65.8%) according to Osteoarthritis Research Society International (OARSI) 2004 criteria. At the end of follow-up, 120 patients responded to IAHA or 22% more than the 100 patients that responded to placebo (relative risk [RR] 1.22, 95% CI 1.07 to 1.41; p=0.004). Adverse events included local bleeding, mild pain, or allergic reaction and occurred at a rate of 0.029 per cycle in both groups. Serious adverse events did not occur. The authors noted repeated injections of IAHA progressively increased the number of patients responding and demonstrated a positive carry-over effect for up to one year but whether this suggests remission or alteration of the course of OA could not be determined.

Two studies from Switzerland compared IAHA with high molecular weight hylan (Synvisc). An RCT compared three injections of either high molecular weight HA (Synvisc), medium molecular weight HA (Orthovisc), or low molecular weight HA (Ostenil, unavailable in the U.S.) in 660 patients with OA of the knee. At six months, there was no difference between groups in any outcome measure. This RCT was one of 13 trials included in the second Swiss study, a meta-analysis that found no superior effectiveness of hylan over hyaluronic acids. In two randomized controlled, non-inferiority trials, published in 2011, different hyaluronan were also compared and
found to have similar outcomes. In one trial of 381 patients, highly purified hyaluronic acid (Sinovial®) was found to be equivalent to 0.8% hylan G-F20 (Synvisc®). In the other trial of 276 patients, a medium molecular weight hyaluronan product (F60027, Structovial) was also found to be equivalent to hylan G-F 20 (Synvisc®).

**Ankle**
The evidence on IAHA injections in the ankle consists of a few small RCTs and case series. DeGroot et al reported on an RCT of 64 patients with ankle OA that compared a single IAHA to a single IA saline injection. At six weeks and 12 weeks, there were no significant differences in improvement between treatment groups on the American Orthopaedic Foot & Ankle Society clinical rating score, the Ankle Osteoarthritis Scale score, and the patient-reported visual analog pain scale (VAS).

Migliore et al conducted a review of seven studies on IAHA for ankle OA, identified from the period of 2006-2009, that included three small RCTs with a total of 75 patients, and four case series. For two of the RCTs, IAHA was compared to saline injection, and the results showed benefit on some outcome measures but not others. The third RCT compared IAHA to exercise therapy and reported no differences in outcomes. The authors were unable to do a meta-analysis due to the limited number of studies and study heterogeneity.

**Foot**
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.

**Hand**
Two small RCTs that enrolled a total of 100 patients evaluated on HA injections compared to steroid injections for arthritis of the thumb. Fuchs et al reported that steroid injections were superior at two to three weeks post-treatment but that IAHA was superior at six month follow-up. Stahl et al reported essentially equivalent outcomes between steroid injections and IAHA, although IAHA was superior to steroids for some aspects of fine motor function. The results of these trials are not sufficient to determine the efficacy of IAHA for thumb arthritis and are not sufficient for determining comparative efficacy to steroids.

**Hip**
One industry-sponsored RCT published since that review compared a single 2.5 mL IAHA (Adant, 900 kDa, unavailable in the U.S.) to saline injection for treatment of hip OA in 85 patients. At three months, there were no significant differences between groups in any outcome measure. The number of patients who experienced mild to moderate treatment-related adverse events (injection-site pain, pain flare, hematoma, pruritus) did not differ between groups.

In another industry-sponsored, single-center, randomized, double-blind, active-controlled trial, published in 2009, forty-two patients with OA of the hip were randomly assigned to receive two monthly injections of high-molecular weight IAHA (Hyalubrix® - unavailable in the U.S.; 1,500-3,200 kDa) or IA mepivacaine, a local anesthetic. At three and six months, there was a
significant decrease in the LFI in the IAHA group compared to the mepivacaine group (5.15 vs. 6.53, respectively, at three months, p<0.001; 3.94 vs. 6.41, respectively, at six months, p<0.05). Of note, two patients with the most severe OA (Kellgren-Lawrence radiologic grade IV) were randomly assigned to the mepivacaine group. The only reported adverse event was injection-site pain occurring in one patient in each group.

Atchia et al reported on a randomized, controlled trial (RCT) of 77 patients with hip OA who were potential candidates for total hip replacement. In this study, patients were randomized to receive standard care or an injection of saline, hyaluronan or methylprednisolone and followed for eight weeks. Significant improvement was only seen in the steroid group in the numerical rating scale for worst pain, and the Western Ontario and McMaster Osteoarthritis Index for pain and function. No improvements were reported in the IAHA group.

**Shoulder**

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.

**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)

**February 2013 Update**

**Knee**

Rutjes et al published a 2012 meta-analysis of 89 trials (12,667 patients) on viscosupplementation for OA of the knee. The main results showed that viscosupplementation
moderately reduced pain (effect size, -0.37). However, several limitations of this body of literature were noted. Trial quality was low, there was considerable between-trial heterogeneity, and an asymmetrical funnel plot suggested publication bias. Five unpublished trials showed an insignificant effect size of -0.03, while analysis of 18 large trials with blinded outcome assessment showed an effect size of -0.11, which is of uncertain clinical significance. Viscosupplementation was also associated with an increased risk for serious adverse events.

A 2012 meta-analysis of 74 trials found that due to the heterogeneity of the studies and outcomes, it was not possible to conclude that one brand is more efficacious than another.

In 2011, the FDA approved the use of a single dose of Gel-One®, a cross-linked formulation of hyaluronic acid. Approval was based on a multicenter randomized double-blind placebo controlled trial in 377 patients. The percentage of patients reporting a 30% or greater improvement in the WOMAC pain subscore was 56.8% at week three compared to 47.2% for placebo. The percentage of patients reporting a 50% or greater improvement in the WOMAC pain subscore was 42.8% at week three compared to 28.0% for placebo. Significant differences between the groups in mean scores persisted throughout the 13 week follow-up period.

There are a large number of RCTs completed on treatment of OA of the knee with HA, and numerous systematic reviews of these trials. The majority of systematic reviews conclude that there is a modest beneficial effect of treatment, and the clinical significance of the magnitude of difference is uncertain. The strength of these conclusions is reduced by limitations in the literature, which include variable quality of studies, a large degree of heterogeneity in outcomes, and possible publication bias. In studies that compared IAHA with IA steroids, IAHA had a slower onset of action and longer duration. Several studies have compared different types of HA, with no clear differences in efficacy found between different types.

**Joints Except the Knee**

Colen et al conducted a 2012 systematic review of prospective trials of IAHA for joints other than the knee. In addition to non-randomized prospective studies, the search identified five RCTs for the hip, one for the shoulder, four for the ankle, five for the carpometacarpal-1 joint, one for the lumbar facet joint, and one for the first metatarsophalangeal joint. Examination of the literature for each joint found evidence for a positive effect of IAHA when compared to baseline, with limited evidence that IAHA is superior to placebo, and no evidence that IAHA is better than corticosteroids or other conservative therapies. Following is a summary of systematic reviews and primary evidence by joint.

**Hip**

In their 2012 systematic review, Colen et al identified three RCTs that compared IAHA with placebo, one that compared IAHA with IA anesthetic, and one that compared hyaluronans of different molecular weights. These three trials showed a statistical effect favoring IAHA treatment. However, the effect size was small compared to saline injections, and there were not significant differences between IAHA and other conservative treatments such as steroid injections.
Shoulder
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.

February 2014 Update
In 2013, Miller et al conducted a systematic review and meta-analysis of randomized saline-controlled trials to determine the safety and efficacy of US-approved intra-articular hyaluronic acid (IAHA) injections for symptomatic knee osteoarthritis. The review included a total of 29 studies (4,866 patients). Compared to pre-injection values, the IAHA injection resulted in very large treatment effects for knee pain and function, with standardized mean difference values 1.07-1.37 (all P<0.001). No statistically different safety outcomes for serious adverse events (SAEs) (P=0.12), treatment-related SAEs (P=1.0), study withdrawal (P=1.0) and adverse event related study withdrawal (P=0.46) were found between IAHA and saline controls. This analysis did address some of the analysis limitations found in prior meta-analyses which brought safety issues under consideration. While this review did note several limitations such as excluding subjects with end-stage knee osteoarthritis, it did include only randomized, saline-controlled trials, structured data extraction methodology, inclusion of all zero total event trials in safety analyses, and sensitivity analyses that accounted for choice of statistical test and potentially influential studies. 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.

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.

**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™

**Approved by Governing Bodies:**
Hyalgan® -FDA approved 05/25/1997
Supartz™-FDA approved 01/24/2001
Orthovisc®-FDA approved 02/04/2004
Euflexxa™-FDA approved 10/20/2005
Synvisc-One™-FDA approved 02/26/2009
Gel-One®-FDA approved 03/22/2011
Monovisc™-FDA approved 02/25/14

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply

**Current Coding:**
CPT codes:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J3490</td>
<td>Unclassified drugs (Effective February 25, 2014)</td>
</tr>
<tr>
<td>J7321</td>
<td>Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose (Effective January 1, 2008)</td>
</tr>
<tr>
<td>J7323</td>
<td>Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose (Effective January 1, 2008)</td>
</tr>
</tbody>
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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)

Previous Coding:
Synvisc-One™ coding - There is currently not a code for Synvisc™
Use: J3490  Unclassified drugs (Effective February 26, 2009 through December 31, 2009)

References:

Policy History:
Medical Policy Group, November 2002
Medical Policy Administration Committee, December 2002
Available for comment December 18, 2002-February 3, 2003
Medical Policy Group, August 2004 (3)
Available for comment August 24-October 7, 2004
Medical Policy Group, October 2004 (3)
Medical Policy Administration Committee, October 2004
Available for comment October 15-November 29, 2004
Medical Policy Group, September 2005 (3)
Available for comment September 26-November 9, 2005
Medical Policy Group, February 2006 (1)
Medical Policy Administration Committee, February 2006
Available for comment March 4-April 17, 2006
Medical Policy Group, December 2007 (3)
Medical Policy Administration Committee, January 2008
Available for comment January 5-February 20, 2008
Medical Policy Group, March 2009 (1)
Medical Policy Administration Committee, March 2009
Available for comment March 18-May 1, 2009
Medical Policy Group, August 2010 (3)
Medical Policy Administration Committee, September 2010
Available for comment September 4-October 18, 2010
Medical Policy Group, October 2010
Medical Policy Group, December 2011 (1): Update to Description, Key Points, Key Words, Approved by Governing Bodies, Coding and References related to Gel One single injection hyaluronan gel
Medical Policy Administration Committee, December 2011
Available for comment December 14, 2011 through January 27, 2012
Medical Policy Group, March 2012 (2): January 2012 Updates – Key Points & References
Medical Policy Panel, February 2013
Medical Policy Group, February 2013 (3): 2013 Updates to Key Points & References; no change in policy statement
Medical Policy Panel, September 2013
Medical Policy Group, February 2014 (3): 2014 Update to Key Points & References; no change in policy statement; added information and reference to address meta-analysis on safety and effectiveness of intra-articular hyaluronic acid injections in patients with knee osteoarthritis
Medical Policy Group, May 2014 (3): added newly FDA-approved Monovisc™ to Description, Governing Bodies, Current Coding sections, & References
Medical Policy Administration Committee, May 2014

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.

Proprietary Information of Blue Cross and Blue Shield of Alabama
Medical Policy #084
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