Clinical Practice Guideline: **Hyaluronan Injections**

Date of Implementation: **August 20, 2015**

Product: **Specialty**

GUIDELINES

Viscosupplementation with hyaluronans will only be covered for osteoarthritis of the knee **upon meeting ALL of the following criteria:**:

1. There is radiological evidence to support the diagnosis of osteoarthritis; and
2. The knee pain interferes with functional activities (e.g., ambulation, prolonged standing); and
3. There is adequate documentation that simple pharmacologic therapy (e.g., acetaminophen), or exercise and physical therapy has been tried and the patient has failed to respond satisfactorily.
4. The individual has experienced an inadequate response or intolerance or contraindications to a trial of intraarticular steroid injections for at least 3 months; and
5. The individual is not scheduled to have a total knee replacement within 6 months of starting treatment.

American Specialty Health – Specialty (ASH) considers all other indications unproven.

The following products have received FDA approval:

1. Hylan G-F 20 [Synvisc ®, Synvisc-One ™]
   - Synvisc ® - (16mg/2ml). The intra-articular injections are given once weekly for a total of three weeks.
   - Synvisc-One™ - (48mg/6ml). The intra-articular injections are given once per six months. Limited to osteoarthritis of the knee.
2. Sodium hyaluronate [Hyalgan ®, Supartz ® or Visco-3™, Euflexxa™, Monovisc™, GelSyn-3™, GenVisc® 850, Durolane®]
   - Hyalgan ® - (20mg/2 ml). The intra-articular injections are given once weekly for a total of five injections.
   - Supartz ® or Visco-3™ - (25mg/2.5 ml). The intra-articular injections are given once a week for a total of five weeks.
   - Euflexxa™ - (20mg/injection). The intra-articular injections are given as a three-injection treatment regimen.
   - Monovisc™ - (88mg/4 ml). The intra-articular injection is given once.
   - GelSyn-3™ - (16.8mg/2mL). The intra-articular injections are given once weekly for three weeks.

- GenVisc® 850 - (25.0mg/3 mL). The intra-articular injection treatment cycle consists of five injections given at weekly intervals.
- Durolane® (3 ml, 20 mg/ml). The intra-articular injections are given once.
- TriVisc™ - (25 mg/2.5 mL). The intra-articular injections are given once weekly x 3 administrations.

3. High molecular weight hyaluronan [Orthovisc ®]
   - Orthovisc ® (30mg/2ml). The intra-articular injections are administered weekly for three - four weeks.
4. Hyaluronic acid [Gel-One®]
   - Gel-One® (30 mg/3 mL). The intra-articular injections are given once.
5. High molecular weight viscoelastic hyaluronan [Hymovis®]
   - Hymovis ® (3 mL). The intra-articular injections are administered two times in two injections one week apart.
6. High molecular weight viscoelastic hyaluronan [SYNOJOYNT ™]
   - SYNOJOYNT ™ (20 mg/2 mL). The intra-articular injections are given once weekly x 3 administrations.
7. High molecular weight hyaluronan [TRILURON ™]
   - TRILURON ™ (20 mg/2 mL). The intra-articular injections are given once weekly x 3 administrations.

Indications For Repeat Courses of Injections

A repeat series of injections may be covered under the following circumstances:

1. The indications above continue to be met; and
2. Significant improvement in pain and functional capacity from the prior series of injections is documented in the medical record; and
3. The last injection (in a prior course) was given at least 6 months ago.

Limitations

If the drug is denied as not reasonable and necessary, the associated injection code will also be denied.

Podiatrists should refer any patients with knee osteoarthritis to a specialist for this procedure, as it is not covered when performed by a podiatrist.

HCPCS Codes and Descriptions

HCPCS Code	HCPCS Code Description
J7318	Hyaluronan or derivative, Durolane, for intra-articular injection, 1 mg
J7320	Hyaluronan or derivative, GenVisc 850, for intra-articular injection, 1 mg

HCPCS Code	HCPCS Code Description
J7321	Hyaluronan or derivative, Hyalgan , Supartz or Visco-3, for intra-articular injection, per dose
J7322	Hyaluronan or derivative, Hymovis, for intra-articular injection, 1 mg
J7323	Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose
J7324	Hyaluronan or derivative, Orthovisc, for intra-articular injection, per dose
J7325	Hyaluronan or derivative, Synvisc or Synvisc-One, for intra-articular injection, 1 mg
J7326	Hyaluronan or derivative, Gel-One, for intra-articular injection, per dose
J7327	Hyaluronan or derivative, Monovisc, for intra-articular injection, per dose
J7328	Hyaluronan or derivative, GELSYN-3, for intra-articular injection, 0.1 mg
J7329	Hyaluronan or derivative, Trivisc, for intra-articular injection, 1 mg
J7331	Hyaluronan or derivative, SYNOJOYNT, for intra-articular injection, 1 mg
J7332	Hyaluronan or derivative, Triluron, for intra-articular injection, 1 mg

GENERAL

Purified natural hyaluronans have been approved by the FDA for the treatment of pain associated with osteoarthritis of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics. The synovial fluid's capacity to lubricate and absorb shock is typically reduced in joints affected by osteoarthritis. These changes are partly due to a reduction in the concentration and size of hyaluronic acid molecules that are naturally present in synovial fluid.

EVIDENCE REVIEW

According to Bellamy et al. (2006), viscosupplementation is an effective treatment for osteoarthritis of the knee with beneficial effects on pain, function, and patient global assessment. The literature suggests that at 5- and 13-weeks post injection, beneficial effects were at their highest level. The magnitude of the clinical effect was different for different products, timepoints variables, and study designs. Therefore, no conclusions can be determined regarding the varying products.

In the AAOS 2nd edition of the Treatment of Osteoarthritis of the Knee Evidence-based Guideline, authors based results on meta-analyses that combined like measurement instruments, which made it possible to determine that the overall effect of hyaluronic acid (HA) did not provide minimum clinically important improvement to patients. These 2nd edition guidelines conclude that HA injections cannot be recommended for treatment of osteoarthritis of the knee. However, the updated 3rd edition (2021) found that statistically significant improvements were associated with high-molecular cross-linked hyaluronic acid but when compared to mid-range molecular weight, statistical significance was not maintained. This newer analysis did not demonstrate clinically relevant differences when compared to controls. However, as previous research reported benefits in their use, the group felt that a specific subset of patients might benefit from its use.

Guidelines on osteoarthritis from the National Institute for Health and Care Excellence (NICE, 2014, reviewed in 2020, and 2022) state: "Do not offer intra-articular hyaluronan injections for the management of osteoarthritis." The 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee (Kolasinski et al. 2020) recommended against (conditionally) for use of hyaluronic acid (HA) injections for the knee and hand and recommend strongly against HA injections for the hip. Bannuru et al. (2019) updated and expanded upon prior Osteoarthritis Research Society International (OARSI) guidelines by developing patient-focused treatment recommendations for individuals with Knee, Hip, and Polyarticular osteoarthritis (OA) that are derived from expert consensus and based on objective review of high-quality meta-analytic data. Core Treatments for Knee OA included arthritis education and structured land-based exercise programs with or without dietary weight management. Core Treatments for Hip and Polyarticular OA included arthritis education and structured land-based exercise programs. Topical non-steroidal anti-inflammatory drugs (NSAIDs) were strongly recommended for individuals with Knee OA (Level 1A). For individuals with gastrointestinal comorbidities, COX-2 inhibitors were Level 1B and NSAIDs with proton pump inhibitors Level 2. For individuals with cardiovascular comorbidities or frailty, use of any oral NSAID was not recommended. Intra-articular (IA) corticosteroids, IA hyaluronic acid, and aquatic exercise were Level 1B/Level 2 treatments for Knee OA, dependent upon comorbidity status, but were not recommended for individuals with Hip or Polyarticular OA. The use of Acetaminophen/Paracetamol (APAP) was conditionally not recommended (Level 4A and 4B), and the use of oral and transdermal opioids was strongly not recommended (Level 5).

Anil et al. (2021) performed a network meta-analysis of the randomized control trials in the literature to ascertain whether there is a superior injectable nonoperative treatment for knee OA. Seventy-nine RCTs with 8,761 patients were included in this review. Intra-articular injectables evaluated included autologous conditioned serum (ACS), bone marrow aspirate concentrate (BMAC), botulinum toxin, corticosteroids (CS), hyaluronic acid (HA), mesenchymal stem cells (MSC), ozone, saline placebo, platelet-rich plasma

(PRP), plasma rich in growth factor (PRGF), and stromal vascular fraction (SVF). At 4-6 weeks and 3 months of follow-up, the treatment with the highest P-Score for WOMAC score was high molecular weight (HMW) HA + CS [P-Score = 0.9500 and 8503, respectively]. At 6-months follow-up, the treatment with the highest P-Score for WOMAC score was PRP [P-Score = 0.7676]. At all post-injection time points, the treatment with the highest P-Score for VAS score [P-Score Range = 0.8631-9927] and Womac score at 12 Months [P-Score = 0.9044] was SVF.

Webner et al. (2021) summarized evidence on the safety and efficacy of intraarticular hyaluronic acid (IAHA) preparations approved in the United States for the treatment of osteoarthritis of the knee. One hundred nine articles meeting our inclusion criteria were identified, including 59 randomized and 50 observational studies. Hylan G-F 20 has been the most extensively studied preparation, with consistent results confirming efficacy in placebo-controlled studies. Efficacy is also consistently reported for Supartz, Monovisc, and Euflexxa, but not for Hyalgan, Orthovisc, and Durolane. In the head-to-head trials, high-molecular-weight (MW) Hylan G-F 20 was consistently superior to low MW sodium hyaluronate preparations (Hyalgan, Supartz) up to 20 weeks, whereas one study reported that Durolane was noninferior to Supartz. Head-to-head trials comparing high versus medium MW preparations all used Hylan G-F 20 as the high MW preparation. Of the IAHA preparations with strong evidence of efficacy in placebo-controlled studies, Euflexxa was found to be noninferior to Hylan G-F 20. There are no direct comparisons to Monovisc. One additional IAHA preparation (i.e., Synovial), which has not been assessed in placebo-controlled studies, was also noninferior to Hylan G-F 20. Authors concluded that IAHA efficacy varies widely across preparations. High-quality studies are required to assess and compare the safety and efficacy of IAHA preparations.

Miller et al. (2021) reported the safety of intra-articular hyaluronic acid (IAHA) in patients with symptomatic knee osteoarthritis (OA). A total of 35 randomized controlled trials with 38 group comparisons comprising 8,078 unique patients (IAHA: 4,295, IA saline: 3,783) were included in the meta-analysis. Comparing IAHA with IA saline over a median of 6 months follow-up, there were no differences in the risk of adverse events (AEs), study withdrawals, or AE-related study withdrawals. Local AEs, all of which were nonserious, were more common with IAHA vs. IA saline and typically resolved within days. Authors concluded that IAHA was shown to be safe for use in patients with symptomatic knee OA. Compared with IA saline, IAHA is associated with an increased risk of nonserious, transient local reactions. There was no evidence to suggest any additional safety risks of IAHA.

Cucurnia et al. (2022) aimed to (1) evaluate clinical outcome after 6 months, (2) evaluate clinical outcomes after 12 months and (3) evaluate clinical outcomes according to OA grade. Patients with symptomatic OA were treated with single intra-articular injection of a high molecular weight, non-cross-linked hyaluronic acid (HA), highly concentrated (2%)

and associated with sorbitol (4%). Hypothesis of the study was that a single intra-articular injection of this HA associated with sorbitol leads to a significant clinical improvement within 6 months in patients with early or moderate knee OA. A total of 77 patients were enrolled in this prospective multicentric study. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score was recorded at baseline and at months 1, 3, 6 and 12 following the intra-articular injection. Seventy-three patients completed the 12 months follow-up. Pain, stiffness, functional limitation, and total scores were significantly reduced at 1, 3 and 6 months, but not at 12 months. Stratified analysis of all subscores according to OA grade showed that pain, functional limitation, and total score decreased at 1, 3, 6 and 12 months in both groups. Stiffness was the only item that decreased significantly at 1, 3 and 6 months but not at 12 months in both groups. All subscore values were significantly lower in the group of patients with low OA grade compared to the one with moderate OA grade. No adverse events were reported. Authors concluded that at 6 months after a single intra-articular injection of a high molecular weight, non-cross-linked HA associated with sorbitol, WOMAC scores decreased significantly. Clinical benefits were observed both in patients with low and in those with moderate OA grade, with better results in the first group.

Documentation Requirements

The patient's medical record should contain documentation that fully supports the medical necessity for intra-articular injections of sodium hyaluronate (Hyalgan®, Supartz® or Visco-3™, Euflexxa™, Monovisc™, GelSyn-3™, GenVisc® 850, Durolane®, TriVisc™, Synojoynt™, Triluron™), hylan G-F 20 (Synvisc®, Synvisc-One ™), hyaluronic acid (Gel-One®), high molecular weight hyaluronan (Orthovisc®) and high molecular weight viscoelastic hyaluronan (Hymovis®) for the treatment of osteoarthritis of the knee or shoulder as it is covered by Medicare (please see "Indications and Limitations of Coverage and/or Medical Necessity"). This documentation includes, but is not limited to, relevant medical history, physical examination and results of pertinent diagnostic tests or procedures, and history of pharmacologic therapy. Documentation of subsequent courses of treatment must clearly establish reduction of patient symptomatology and medication usage. This documentation must be submitted upon request. Claims submitted without requested supporting evidence in the medical record will be denied as being not medically necessary.

Utilization

The dose and frequency of administration should be consistent with the FDA approved labeling.

It is expected that an injection (Synvisc-One ™, Gel-One®, Durolane®) or course of the injections (Synvisc®, Hyalgan®, Supartz® or Visco-3™, Euflexxa™, Orthovisc®, GelSyn-3™, GenVisc® 850, Hymovis®, TriVisc™, Synojoynt™, Triluron™) will not be repeated within 6 months-time.

Coding information

1. If an aspiration and an injection procedure are performed at the same session, bill only one unit for CPT code 20610 or 20611.
2. The appropriate site modifier (RT or LT) must be appended to CPT code 20610 or 20611 to indicate if the service was performed unilaterally and modifier (50) must be appended to indicate if the service was performed bilaterally.
3. Use "EJ" modifier on drug codes to indicate subsequent injections of a series. Do not use this modifier for the first injection of each series. A series is defined as the set of injections for each joint and each treatment. Injection of the left is a separate series from injection of the right knee.

Codes and Descriptions

CPT® Code	CPT® Code Description
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

ICD-10 Codes and Descriptions

ICD-10 Code	ICD-10 Code Description
M17.0	Bilateral primary osteoarthritis of knee
M17.11	Unilateral primary osteoarthritis, right knee
M17.12	Unilateral primary osteoarthritis, left knee
M17.2	Bilateral post-traumatic osteoarthritis of 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

PRACTITIONER SCOPE AND TRAINING

Practitioners should practice only in the areas in which they are competent based on their education, training, and experience. Levels of education, experience, and proficiency may vary among individual practitioners. It is ethically and legally incumbent on a practitioner to determine where they have the knowledge and skills necessary to perform such services and whether the services are within their scope of practice.

It is best practice for the practitioner to appropriately render services to a member only if they are trained, equally skilled, and adequately competent to deliver a service compared to others trained to perform the same procedure. If the service would be most competently delivered by another health care practitioner who has more skill and training, it would be best practice to refer the member to the more expert practitioner.

Best practice can be defined as a clinical, scientific, or professional technique, method, or process that is typically evidence-based and consensus driven and is recognized by a majority of professionals in a particular field as more effective at delivering a particular outcome than any other practice (Joint Commission International Accreditation Standards for Hospitals, 2020).

Depending on the practitioner's scope of practice, training, and experience, a member's condition and/or symptoms during examination or the course of treatment may indicate the need for referral to another practitioner or even emergency care. In such cases it is prudent for the practitioner to refer the member for appropriate co-management (e.g., to their primary care physician) or if immediate emergency care is warranted, to contact 911 as appropriate. See the *Managing Medical Emergencies (CPG 159 – S)* clinical practice guideline for information.

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