MEDICAL MUTUAL®

Drug Policy

Policy:	**99002**	**Initial Effective Date: 05/07/1999** **Annual Review Date: 08/16/2018** **Last Revised Date: 12/26/2018**
Code(s):	**HCPCS C9465, J7318, J7320, J7321, J7322, J7323, J7324, J7325, J7326, J7327, J7328, J7329**	
SUBJECT:	**Hyaluronic acid derivatives, intraarticular** • Durolane® (sodium hyaluronate injection- Bioventus) • **Euflexxa™ (sodium hyaluronate injection – Ferring Pharmaceuticals)*†** • Gel-One® (sodium hyaluronate injection – Seikagak Corporation/Zimmer) • Gelsyn-3™ (sodium hyaluronate injection – IBSA) • GenVisc® 850 (sodium hyaluronate injection – OrthogenRx) • Hyalgan® (sodium hyaluronate injection - sanofi-aventis) • Hymovis® (high molecular weight viscoelastic hyaluronan injection – Fidia, Pharma USA) • Monovisc™ (high molecular weight hyaluronan injection – Depuy Mitek/Johnson & Johnson) • Orthovisc® (high molecular weight hyaluronan injection – DePuy Mitek/Johnson&Johnson) • Supartz™ (sodium hyaluronate injection – Smith & Nephew) • **Synvisc® (hylan G-F 20 sodium hyaluronate injection – Genzyme)*** • **Synvisc-One™ (hylan G-F 20 sodium hyaluronate injection – Genzyme)*** • TriVisc™ (sodium hyaluronate injection – OrthogenRx) • Visco-3™ (sodium hyaluronate injection- Zimmer Biomet)	

***Euflexxa and Synvisc/Synvisc-One are the preferred hyaluronic acid derivative products for commercial members**

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

Overview

Hyaluronic acid derivatives (HADs) are indicated for the treatment of pain related to knee osteoarthritis (OA) in patients who have failed to respond adequately to conservative nonpharmacologic therapy and to simple analgesics (e.g., acetaminophen).[1-10] The use of intra-articular (IA) injections of HADs are to restore the normal properties (viscosity and elasticity) of the synovial fluid. Other effects of these products have been noted,

which include free radical scavenging and antinociceptive effects.[11] It should be noted that Euflexxa, Gel-Syn, GenVisc 850, Hymovis, Monovisc, and Orthovisc are the only products derived from non-avian sources (they are derived from bacterial cells).[5-6,8-10] These products may be preferred in patients with allergies to avian proteins and products (e.g., eggs, feathers). GenVisc 850 has data to support similarity to Supartz/Supartz FX.[9]

Product	Directions for Use, Intra-articular	How Supplied (dose is per knee)
Durolane	1 injection	Single-use 3 ml glass syringe. 20 mg sodium hyaluronate/mL
Euflexxa	3 injections given one week apart.	Single-use 2.25 mL glass syringe. 20 mg sodium hyaluronate/2 mL.
Gel-One	1 injection	Single-use 3 mL prefilled syringe. 30 mg cross-linked hyaluronate/3 mL.
Gelsyn-3	IA injection (2 mL) QW for 3 weeks.	Single-use 2 mL prefilled syringe. 16.8 mg sodium hyaluronate/2 mL.
GenVisc 850	5 injections given one week apart. Some patients may benefit from 3 injections.	Single-use 3 mL prefilled syringe. 25 mg sodium hyaluronate/2.5 mL.
Hyalgan	5 injections given one week apart. Some patients may benefit from 3 injections.	Single-use 2 mL vials and prefilled syringes. 20 mg sodium hyaluronate/2 mL.
Hymovis	1 injection weekly for 2 weeks	Single-use 3 mL injection in a 5-mL syringe 8 mg hyaluronan per 1 mL (24 mg/3 mL)
Monovisc	1 injection	Single-use 5 mL syringe. 88 mg hyaluronan/4 mL.
Orthovisc	3 or 4 injections given one week apart.	Single-use 3 mL syringe. 30 mg hyaluronan/2 mL.
Synvisc	3 injections given one week apart.	Single-use 2.25 mL glass syringe. 16 mg hylan polymers/2 mL.
Synvisc-One	1 injection.	Single-use 10 mL glass syringe. 48 mg hylan polymers/6 mL.
Supartz/Supartz FX	5 injections given one week apart. Some patients may benefit from 3 injections.	Single-use 2.5 mL prefilled syringe. 25 mg sodium hyaluronate/2.5 mL.
TriVisc	Three injections given 1 week apart	Single-use 2.5 mL prefilled syringe
Visco-3	3 injections given one week apart for 3 weeks	Single-use 2.5 mL prefilled syringe (1.0% solution[10 mg/mL] 25mg total sodium hyaluronate (hyaluronan)

Guidelines

Guidelines for the medical management of OA of the hand, hip, and knee were published in 2012 by the American College of Rheumatology (ACR).[12] Initial pharmacologic therapy for knee OA consists of acetaminophen, oral and topical non-steroidal anti-inflammatory drugs (NSAIDs), tramadol, and IA corticosteroid injections. IA HA, duloxetine, and opioids are recommended in certain conditions, including patients who failed to respond to initial therapies for ***knee*** OA. IA HA is not recommended in patients with

hand or hip OA. In the guidelines, no distinction is made between the available IA HA products or between products with various molecular weights.

The American Academy of Orthopaedic Surgeons (AAOS) updated guidelines (2013) for the treatment of OA of the knee (non-arthroplasty) mention HA derivatives.[13] However, the guidelines note that HA cannot be recommended for patients with symptomatic OA of the knee. This recommendation is based on an analysis that included 14 studies demonstrating that the effect of HA injections was unlikely to provide a clinically important benefit based on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and visual analog scale (VAS) pain and WOMAC function on the basis of age, baseline pain scores, body mass index (BMI), weight, and gender. AAOS noted that when the high- and low-molecular weight products were analyzed, most of the statistically significant outcomes were associated with the high-molecular cross-linked HA, but when compared to mid-range molecular weight products, statistical significance was not maintained. The guidelines specifically note that treatment comparisons between any weights higher than 750 kDa were not significantly different. It is also noted that other reviews (e.g., by the Agency for Healthcare Research and Quality [AHRQ]) demonstrate a statistically significant treatment effect using different selection criteria. AAOS acknowledges that lower-strength studies were excluded from the AAOS review based on selection criteria, and states that other agencies have acknowledged that there is evidence of potential publication bias with HA products.

The OA Research Society International (OARSI) also has guidelines for knee OA (2014).[14] Based on good evidence from systematic reviews and meta-analyses of randomized controlled trials, these multidisciplinary guidelines note that use of IA HA is uncertain in knee OA and not appropriate for multiple-joint OA. It was noted that inconsistent conclusions among the meta-analyses and conflicting results regarding safety influenced the recommendation.

Policy Statement

This policy involves the use of hyaluronic acid derivative (HAD) products. Prior authorization is recommended for medical benefit coverage of HAD products. Coverage is recommended for those who meet the conditions of coverage in the **Criteria, Dosing, Initial/Extended Approval, Duration of Therapy, and Labs/Diagnostics** for the diagnosis provided. The requirement that the patient meet the Criteria for coverage of the requested medication applies to the initial authorization only. **Waste Management** applies for all covered conditions. **Conditions Not Recommended for Approval** are listed following the Recommended Authorization Criteria and Waste Management section.

Because of the of the specialized skills required for evaluation and diagnosis of patients treated with HAD products as well as the specialized administration technique, these products are required to be administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist) or a physician who has received specific training in the administration and use of viscosupplements. Previous therapy is required to be verified by a clinician in the Coverage Review Department when noted in the criteria as **[verification of therapies required].** All approvals for initial therapy

are provided for the number of injections noted below. If at least 6 months have elapsed since the last injection with any HAD product and the patient has responded to therapy, a repeat course may be authorized (see criteria below).

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of hyaluronic acid derivatives is recommended in those who meet one of the following criteria:

Food and Drug (FDA)-Approved Indications

1. Osteoarthritis (OA) of the Knee.

Criteria. *Patient must meet the following criteria (a, b, c, and d)*:

a) Diagnosis of the knee to be treated is confirmed by radiologic evidence of knee OA (e.g., x-ray, magnetic resonance imaging [MRI], computed tomography [CT] scan, ultrasound); AND

b) The patient has tried at least TWO of the following three modalities of therapy for OA (i, ii, iii):[12]

i. At least one course of physical therapy (PT) for knee osteoarthritis; OR

ii. At least TWO of the following pharmacologic therapies: **[verification of therapies required]**:

1. NSAIDs (oral [e.g., naproxen, ibuprofen] or topical [Pennsaid® solution or Voltaren® gel], Celebrex® (celecoxib)) [NOTE: a trial of two or more NSAIDs counts as one pharmacologic therapy],\
2. acetaminophen
3. tramadol
4. Duloxetine (Cymbalta, generics); [12]

iii. At least TWO injections of IA corticosteroids to the affected knee; AND

c) The product is administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist) or a physician who has received specific training in the administration and use of viscosupplements; AND

d) If the request is for a hyaluronic acid derivative other than a preferred HAD agent, patient must have a documented failure, contraindication, intolerance or ineffective response with a minimum 3 month trial of BOTH preferred HAD agents (Euflexxa and Synvisc/Synvisc-One).*

***Euflexxa and Synvisc/Synvisc-One are the preferred HAD products for commercial members. Patient must have a documented failure, contraindication, intolerance, or ineffective response with a minimum 3 month trial of BOTH preferred products for a non-preferred HAD product to be considered for approval.**

These preparations are indicated for the treatment of pain related to knee OA for patients who have failed to adequately respond to other therapies (i.e., nonpharmacologic therapy, analgesics).[1-8] Many other pharmacologic therapies are approved and available for the treatment of knee OA. Guidelines for the medical management of OA of the hand, hip, and knee were published in 2012 by the American College of Rheumatology (ACR).[12] Initial pharmacologic therapy for knee OA consists of acetaminophen, oral and topical non-steroidal anti-inflammatory drugs (NSAIDs), tramadol, and IA corticosteroid injections. IA HA, Cymbalta® (duloxetine), and opioids are

recommended in certain conditions, including patients who failed to respond to initial therapies for *knee* OA. IA HA is not recommended in patients with hand or hip OA. In the guidelines, no distinction is made between the available IA HA products or between products with various molecular weights. In the professional opinion of specialist physicians reviewing the data, we have adopted the requirement for confirmation of diagnosis by radiologic evidence.

Dosing in Osteoarthritis of the Knee. *Dosing must meet the following for the requested product*:[1-10]

Product	Number of injections per course
Durolane	1 injection given one time
Euflexxa	3 injections given one week apart.
Gel-One	1 injection given one time
Gelsyn-3	Three injections given 1 week apart
GenVisc 850	Five injections given 1 week apart
Hyalgan	5 injections given one week apart.
Hymovis	2 injections given one week apart.
Monovisc	1 injection given one time
Orthovisc	3 or 4 injections given one week apart.
Synvisc	3 injections given one week apart.
Synvisc-One	1 injection given one time
Supartz/Supartz FX	5 injections given one week apart.
TriVisc	3 injections given one week apart
Visco-3	3 injections given one week apart

*Dose is for one knee. If two knees are being treated, then each knee requires a syringe or vial of product.

Initial Approval.[1-10]

Product	Number of injections (doses) per course per knee
Durolane	1 injection
Euflexxa	3 injections
Gel-One	1 injection
Gelsyn-3	Three injections
GenVisc 850	Five injections (some will only use three)

Hyalgan	5 injections (some will only use 3)
Hymovis	2 injections
Monovisc	1 injection
Orthovisc	3 or 4 injections
Synvisc	3 injections
Synvisc-One	1 injection
Supartz/ Supartz FX	5 injections (some will only use 3)
TriVisc	3 injections
Visco-3	3 injections

Extended Approval. *A repeat course can be authorized if the patient meets the following criteria (a, b, AND c):*

a) At least 6 months have elapsed since the last injection with hyaluronic acid derivatives; AND

b) The patient had a response to the previous course of therapy for osteoarthritis of the knee (e.g., reduced joint pain, tenderness, or morning stiffness, improved mobility) according to the prescribing physician and now requires additional therapy for osteoarthritis symptoms; AND

c) The product is administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist) or a physician who has received specific training in the administration and use of viscosupplements.

Although retreatment data are limited, all of the HAD products have data concerning efficacy and/or safety of repeat courses.[1-10,15] In many cases, at least 6 months was required or a minimum of 6 months had elapsed prior to injection of a repeat course.[3,5-6,9,16-17] In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirement for repeat courses.

Duration of Therapy. Duration of therapy varies depending on product. The course may be repeated if the patient had a response to the previous course.

Labs/Diagnostics. For initial approval, radiologic evidence of osteoarthritis of the affected knee is required as noted in the criteria section.

Waste Management.

The number of injections depends on which product is used. The entire vial or syringe is injected. If both knees are being treated then two syringes/vials will be needed.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Hyaluronic acid derivatives have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions are provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Acute Ankle Sprain.** A randomized, controlled, prospective trial was conducted which assessed the use of IA HA in acute ankle sprains.[18-19] Patients treated with IA HA (n = 79) within 48 hours of injury and again on Day 4 reported a time to pain-free and disability-free return to sport of 11 days (± 8 days) compared with 17 days (± 8 days) for placebo ($P < 0.05$).[18] All patients were also treated with standard of care (rest, ice, compression, and elevation [RICE]). At 24 months, the placebo group experienced an increase in repeat sprains when compared with those treated with HA (21 recurrent ankle sprains in the placebo group compared with 7 recurrent ankle sprains in the HA treatment group [$P < 0.001$]) as well as a significant difference in missed days from participation in sport activity (49 days vs. 12 days for the placebo and HA groups, respectively; $P < 0.001$).[19] More data are needed to determine the role of IA HA products in the treatment of acute ankle sprains.

2. **OA and Other Pathologic Conditions Involving Joints Other than the Knee (**e.g., hand, hip, ankle, shoulder OA, temporomandibular joint [TMJ], adhesive capsulitis of the shoulder, subacromial impingement). The prescribing information for these agents state in the precautions section that the safety and effectiveness of hyaluronic acid derivatives injections into joints other than the knee have not been established.[1-10] Due to the absence of evidence to support use of IA HA and potential for harm, the guidelines for the management of hand, hip, and knee OA by ACR (2012) do not recommend use of IA HA in patients with hand or hip OA.12 AAOS has published guidelines that mention HA as an option for glenohumoral (shoulder) joint OA.20 The guidelines note that the strength of evidence for using HA to treat this joint is weak even though each outcome in the single study evaluated did result in statistically significant improvement in pain relief, range of motion, and quality of life for patients with shoulder pain. Small trials have also investigated IA HA in other joints, including ankle OA21-28 and hip OA.[29-36] More data are needed to determine if there is a role for IA HA for the treatment of OA involving other joints. A small trial (n = 70) found that IA HA did not result in increased benefit for adhesive capsulitis of the shoulder (also known as frozen shoulder) in patients who were already receiving PT.37 Another small study (n = 159) did not show benefit of IA HA over corticosteroid or placebo injections in patients with subacromial impingement.[38]

3. **Pathologic Conditions of the Knee Other than OA** [e.g., chondromalacia patellae, osteochondritis dissecans, patellofemoral syndrome, post-anterior cruciate ligament {ACL} reconstruction]. HA products are indicated in knee OA.[1-10] Adequate, well-designed trials have not clearly established the use of IA HA in other conditions of the knee.[39-40]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Documentation Requirements:

The Company reserves the right to request additional documentation and to deny reimbursement when it has determined that the services performed were not medically necessary, investigational and/or a pattern of practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

Prior approval is required for HCPCS Codes C9465, J7318, J7320, J7321, J7322, J7323, J7324, J7325, J7326, J7327, J7328, J7329

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Other References Utilized

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HCPCS Code(s):	
C9465	Hyaluronan or derivative, Durolane, for intra-articular injection, per dose
J7318	Hyaluronan or derivative, durolane, for intra-articular injection, 1 mg
J7320	Hyaluronan or derivative, Genvisc 850, for intra-articular injection, 1 mg
J7321	Hyaluronan or derivative, Hyalgan, Supartz or Visco-3, for intra-articular injection, per dose
J7322	Hyaluronan or derivative, Hymovis, for intra-articular injection, 1 mg
J7323	Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose
J7324	Hyaluronan or derivative, Orthovisc, for intra-articular injection, per dose
J7325	Hyaluronan or derivative, Synvisc or Synvisc-One for intra-articular injection, 1mg
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, per 0.1 mg
J7329	Hyaluronan or derivative, trivisc, for intra-articular injection, 1 mg