

POLICY: Hyaluronic acid derivatives, intraarticular

- Durolane[®] (sodium hyaluronate injection – Bioventus)
- Euflexxa[®] (sodium hyaluronate injection – Ferring Pharmaceuticals)
- Gel-One[®] (sodium hyaluronate injection – Seikagaku Corporation/Zimmer)
- Gelsyn-3[™] (sodium hyaluronate injection – IBSA)
- GenVisc[®] 850 (sodium hyaluronate injection – OrthogenRx)
- Hyalgan[®] (sodium hyaluronate injection – Fidia Pharma)
- 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 FX[™] (sodium hyaluronate injection – Smith & Nephew)
- Sodium hyaluronate 1% injection – Teva
- Synvisc[®] (hylan G-F 20 sodium hyaluronate injection – Genzyme)
- Synvisc-One[®] (hylan G-F 20 sodium hyaluronate injection – Genzyme)
- Triluron[™] (sodium hyaluronate injection – Fidia Pharma)
- TriVisc[™] (sodium hyaluronate injection – OrthogenRx)
- Visco-3[™] (sodium hyaluronate injection – Seikagaku Corporation/Bioventus)

APPROVAL DATE: 07/31/2019

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).¹⁻¹⁶ The use of intra-articular (IA) injections of HADs are to restore the normal properties (viscosity and elasticity) of the synovial fluid. Gel-One, Hyalgan, Supartz FX, Synvisc/Synvisc-One, Triluron, and Visco-3 are derived from rooster or chicken combs. The remaining products are derived from non-avian sources and may be useful for patients with allergies to eggs or poultry products. GenVisc 850 has data to support similarity to Supartz FX.⁹ All of the products given as a series of five injections (GenVisc 850, Hyalgan, and Supartz FX) have a corresponding product that is equivalent to three injections (TriVisc, Triluron, and Visco-3, respectively). Although retreatment data are limited, all of the HAD products have data concerning efficacy and/or safety of repeat courses. In many cases, at least 6 months was required or a minimum of 6 months had elapsed prior to injection of a repeat course.

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).¹⁷ 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.¹⁸ 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).¹⁹ These 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 meta-analyses and conflicting results regarding safety influenced the recommendation.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of hyaluronic acid derivatives indicated for knee OA. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. 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). Previous therapy is required to be verified by a clinician when noted in the criteria as **[verification of therapies required]**. All approvals for initial therapy are provided for the number of injections noted below.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

- 1. Osteoarthritis (OA) of the Knee.** Approve one course of therapy per treated knee if the patient meets ONE of the following conditions (A or B):
 - A) Initial Therapy.** Approve an initial course if the patient meets ALL of the following conditions (i, ii, and iii):
 - i.** 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

- ii. The patient has tried at least TWO of the following three modalities of therapy for OA (i, ii, iii):
 - a) At least one course of physical therapy (PT) for knee osteoarthritis; OR
 - b) At least TWO of the following pharmacologic therapies [(1), (2), (3), (4)] **[verification of therapies required]:**
 - (1) Nonsteroidal anti-inflammatory drug (NSAID), oral or topical (examples of oral agents include naproxen, ibuprofen, Celebrex[®] [celecoxib capsules]; examples of topical NSAIDs include: diclofenac solution [e.g., Pennsaid[®]] or diclofenac 1% gel [e.g., Voltaren[®] gel]) [NOTE: a trial of two or more NSAIDs {oral and/or topical} counts as one pharmacologic therapy];
 - (2) Acetaminophen;
 - (3) Tramadol (Ultram[®]/XR, generics);
 - (4) Duloxetine (Cymbalta[®], generics);
 - c) At least TWO injections of IA corticosteroids to the affected knee; AND
 - iii. The product is administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist).
- B) Patient has Already Received a Course of HAD in the Same Knee.** Approve ONE repeat course if the patient meets ALL of the following conditions (i, ii, and iii):
- i. At least 6 months have elapsed since the last injection with any hyaluronic acid derivative (HAD); AND
 - ii. The patient had a response to the previous course of hyaluronic acid derivative (HAD) 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
 - iii. The product is administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist).

Dosing. Approve the following dosing regimens:

- A) **Durolane, Gel-One, Monovisc, Synvisc-One:** Approve one injection.
 - B) **Hymovisc:** Approve up to two injections given 1 week apart.
 - C) **Euflexxa, Gelsyn-3, sodium hyaluronate 1% injection, Synvisc, Triluron, TriVisc, Visco-3:** Approve up to three injections given 1 week apart.
 - D) **Orthovisc:** Approve up to 4 injections given 1 week apart.
 - E) **GenVisc 850, Hyalgan, Supartz FX:** Approve up to 5 injections given 1 week apart.
- Note: Dose listed is for one knee. If two knees are being treated, then each knee requires a syringe or vial of product

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 of these specific conditions is 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.²⁰⁻²¹ 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 (\pm 8 days) compared with 17 days (\pm 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).²¹ More data are needed to determine the role of IA HA products in the treatment of acute ankle sprains.

2. **Osteoarthritis (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.¹⁻¹⁶ 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.¹⁷ AAOS has published guidelines that mention HA as an option for glenohumeral (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 OA and hip OA.²³⁻³⁸ 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.³⁹ Another small study (n = 159) did not show benefit of IA HA over corticosteroid or placebo injections in patients with subacromial impingement.⁴⁰
3. **Pathologic Conditions of the Knee Other than Osteoarthritis (OA)** [e.g., chondromalacia patellae, osteochondritis dissecans, patellofemoral syndrome, post-anterior cruciate ligament {ACL} reconstruction]. HA products are indicated in knee OA.¹⁻¹⁶ Adequate, well-designed trials have not clearly established the use of IA HA in other conditions of the knee.⁴¹⁻⁴²
4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Durolane [prescribing information]. Durham, NC: Bioventus; not dated. Accessed on July 25, 2019. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170007D.pdf.
 2. Euflexxa[®] injection [prescribing information]. Parsippany, NJ: Ferring Pharmaceuticals, Inc.; July 2016.
 3. Gel-One[®] injection [prescribing information]. Warsaw, IN: Zimmer; May 20, 2011.
 4. Gelsyn-3 [prescribing information]. Durham, NC: Bioventus; 2016.
 5. GenVisc[®] 850 [prescribing information]. Doylestown, PA: OrthogenRx; not dated. Accessed on July 25, 2019. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140005d.pdf.
 6. Hyalgan[®] injection [prescribing information]. Parsippany, NJ: Fidia Pharma USA Inc; May 2014.
 7. Hymovis[®] [prescribing information]. Parsippany, NJ: Fidia Pharma USA; October 2015.
 8. Monovisc[®] [prescribing information]. Bedford, MA: DePuy Mitek, Inc./Johnson & Johnson/Anika Therapeutics; not dated. Accessed on July 25, 2019. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf9/p090031c.pdf.
 9. Orthovisc[®] injection [prescribing information]. Raynham, MA: DePuy Mitek/Anika Therapeutics/Johnson & Johnson; September 2014. Accessed on July 25, 2019. Available at: <http://synthes.vo.llnwd.net/o16/LLNWMB8/US%20Mobile/Synthes%20North%20America/Product%20Support%20Materials/Brochures/Orthovisc%20Physician%20Brochure%20Final%209-14.pdf>.
 10. Sodium hyaluronate 1% injection [prescribing information]. North Wales, PA: Teva; March 2019.
 11. Supartz[®] FX[™] [prescribing information]. Durham, NC: Bioventus; April 2015.
-

12. Synvisc® injection [prescribing information]. Ridgefield, NJ: Genzyme Biosurgery; September 2014.
 13. Synvisc-One® injection [prescribing information]. Ridgefield, NJ: Genzyme Biosurgery; September 2014.
 14. Triluron [prescribing information]. Florham Park, NJ: Fidia Pharma; March 2019.
 15. Trivisc [prescribing information]. Doylestown, PA: OrthogenRx; not dated. Accessed on July 25, 2019. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160057D.pdf.
 16. Visco-3 [prescribing information]. Durham, NC: Bioventus; not dated. Accessed on July 25, 2019. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf/p980044s027d.pdf.
 17. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res.* 2012;64:465-474.
 18. Jevsevar D, Brown GA, Jones DL, et al. Treatment of osteoarthritis of the knee, 2nd edition: summary of recommendations. May 18, 2013. Available at: <http://www.aaos.org/research/guidelines/guidelineoaknee.asp>. Accessed on July 25, 2019.
 19. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage.* 2014;22(3):363-388.
 20. Petrella RJ, Petrella MJ, Cogliano A. Periarticular hyaluronic acid in acute ankle sprain. *Clin J Sport Med.* 2007;17(4):251-257.
 21. Petrella MJ, Cogliano A, Petrella RJ. Original research: long-term efficacy and safety of periarticular hyaluronic acid in acute ankle sprain. *Phys Sportsmed.* 2009;37(1):64-70.
 22. Izquierdo R, Voloshin I, Edwards S, et al. Treatment of glenohumeral osteoarthritis. *J Am Acad Orthop Surg.* 2010;18(6):375-382.
 23. Sun SF, Chou YJ, Hsu CW, et al. Efficacy of intra-articular hyaluronic acid in patients with osteoarthritis of the ankle: a prospective study. *Osteoarthritis Cartilage.* 2006;14(9):867-874.
 24. Salk RS, Chang TJ, D'Costa WF, et al. Sodium hyaluronate in the treatment of osteoarthritis of the ankle: a controlled, randomized, double-blind, pilot study. *J Bone Joint Surg Am.* 2006;88(2):295-302.
 25. Karatosun V, Unver B, Ozden A, et al. Intra-articular hyaluronic acid compared to exercise therapy in osteoarthritis of the ankle. A prospective randomized trial with long-term follow-up. *Clin Exp Rheumatol.* 2008;26(2):288-294.
 26. Sun SF, Chou YJ, Hsu CW, Chen WL. Hyaluronic acid as a treatment for ankle osteoarthritis. *Curr Rev Musculoskelet Med.* 2009;2(2):78-82.
 27. Cohen MM, Altman RD, Hollstrom R, et al. Safety and efficacy of intra-articular sodium hyaluronate (Hyalgan) in a randomized, double-blind study for osteoarthritis of the ankle. *Foot Ankle Int.* 2008;29(7):657-663.
 28. Abate M, Pulcini D, Di Iorio A, Schiavone C. Viscosupplementation with intra-articular hyaluronic acid for treatment of osteoarthritis in the elderly. *Curr Pharm Des.* 2010;16(6):631-640.
 29. DeGroot H 3rd, Uzunishvili S, Weir R, et al. Intra-articular injection of hyaluronic acid is not superior to saline solution injection for ankle arthritis: a randomized, double-blind, placebo-controlled study. *J Bone Joint Surg Am.* 2012;94(1):2-8.
 30. Sun SF, Hsu CW, Sun HP, et al. The effect of three weekly intra-articular injections of hyaluronate on pain, function, and balance in patients with unilateral ankle arthritis. *J Bone Joint Surg Am.* 2011;93(18):1720-1726.
 31. Tikiz C, Unlu Z, Sener A, et al. Comparison of the efficacy of lower and higher molecular weight viscosupplementation in the treatment of hip osteoarthritis. *Clin Rheumatol.* 2005;24:244-250.
 32. Migliore A, Tormenta S, Severino L, et al. The symptomatic effects of intra-articular administration of hylan G-F 20 on osteoarthritis of the hip: clinical data of 6 months follow-up. *Clin Rheumatol.* 2006;25(3):389-393.
 33. Qvistgaard E, Christensen R, Torp-Pedersen S, Bliddal H. Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. *Osteoarthritis Cartilage.* 2006;14(2):163-170.
 34. Caglar-Yagci H, Unsal S, Yagci I, et al. Safety and efficacy of ultra-sound guided intra-articular hylan G-F 20 injection in osteoarthritis of the hip: a pilot study. *Rheumatol Int.* 2005;25(5):341-344.
 35. Conrozier T, Vignon E. Is there evidence to support the inclusion of viscosupplementation in the treatment paradigm for patients with hip osteoarthritis? *Clin Exp Rheumatol.* 2005;23(5):711-716.
 36. Van Den Bekerom MPJ. Viscosupplementation in symptomatic severe hip osteoarthritis: a review of the literature and report on 60 patients. *Acta Orthop Belg.* 2006;72:560-568.
 37. Fernandez Lopez JC, Ruano-Ravina A. Efficacy and safety of intraarticular hyaluronic acid in the treatment of hip osteoarthritis: a systematic review. *Osteoarthritis Cartilage.* 2006;14(12):1306-1311.
 38. Richette P, Ravaud P, Conrozier T, et al. Effect of hyaluronic acid in symptomatic hip osteoarthritis: a multicenter, randomized, placebo-controlled trial. *Arthritis Rheum.* 2009;60(3):824-830.
 39. Hsieh LF, Hsu WC, Lin YJ, et al. Addition of intra-articular hyaluronate injection to physical therapy program produces no extra benefits in patients with adhesive capsulitis of the shoulder: a randomized controlled trial. *Arch Phys Med Rehabil.* 2012;93(6):957-964.
 40. Penning LI, de Bie RA, Walenkamp GH. The effectiveness of injections of hyaluronic acid or corticosteroid in patients with subacromial impingement: a three-arm randomised controlled trial. *J Bone Joint Surg Br.* 2012;94(9):1246-1252.
 41. Tang X, Pei FX, Zhou ZK, et al. A randomized, single-blind comparison of the efficacy and tolerability of hyaluronate acid and meloxicam in adult patients with Kashin-Beck disease of the knee. *Clin Rheumatol.* 2012;31(7):1079-1086.
-

42. Chau JY, Chan WL, Woo SB, et al. Hyaluronic acid instillation following arthroscopic anterior cruciate ligament reconstruction: a double-blinded, randomised controlled study. *J Orthop Surg (Hong Kong)*. 2012;20(2):162-165.

HISTORY

Type of Revision	Summary of Changes	Approval Date
Early annual revision	Add [verification of therapies required] for previous pharmacological therapies which must be reviewed by a clinician.	03/08/2017
Selected revision	Add Durolane to the policy with an approval of one dose.	10/18/2017
Early annual revision	Add TriVisc and Visco-3 to the policy with the same criteria as other agents. Approval is for one course (3 injections).	02/07/2018
Early annual revision	Add Synojoynt to the policy with the same criteria as other agents. Approval is for one course (3 injections).	10/31/2018
Early annual revision	Throughout the policy, replace reference to Synojoynt with sodium hyaluronate 1% (aligns with how product is marketed in the US). Remove Supartz from the policy (obsolete). Osteoarthritis of the Knee: For products given as a series of injections, update approval language to say that approval is for “up to” the maximum number of injections per course.	07/31/2019