

- POLICY:** Hyaluronic Acid Derivatives Intraarticular Utilization Management Medical Policy
- Durolane[®] (sodium hyaluronate injection – Bioventus)
 - 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
 - SynoJoynt[™] (sodium hyaluronate injection – Arthrex)
 - Triluron[™] (sodium hyaluronate injection – Fidia Pharma)
 - TriVisc[™] (sodium hyaluronate injection – OrthogenRx)
 - Visco-3[™] (sodium hyaluronate injection – Seikagaku Corporation/Bioventus)

EFFECTIVE DATE: 1/1/2022

LAST REVIEW DATE: 07/27/2022

COVERAGE CRITERIA FOR: UCare Medicare Plans Only (UCare Medicare, UCare Medicare with M Health Fairview and North Memorial, EssentiaCare, Group Plans, MSHO, Connect + Medicare)

OVERVIEW

Hyaluronic acid derivatives are indicated for the treatment of pain related to knee osteoarthritis in patients who have failed to respond adequately to conservative nonpharmacologic therapy and to simple analgesics (e.g., acetaminophen).¹⁻¹⁶ The use of intraarticular injections 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 these 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 osteoarthritis of the hand, hip, and knee are available from the American College of Rheumatology (2019).¹⁷ Multiple non-pharmacological modalities are recommended for knee osteoarthritis, including exercise, self-management programs, weight loss, Tai Chi, and use of assistive devices (i.e., bracing or a cane). Pharmacologic therapy for knee osteoarthritis consists of acetaminophen, oral and topical non-steroidal anti-inflammatory drugs (NSAIDs), tramadol, intraarticular corticosteroid injections, duloxetine, and topical capsaicin. There is limited evidence establishing a benefit of hyaluronic acid intraarticular injections, which contributes to the conditional recommendation against

use in knee osteoarthritis. However, when other alternatives have been exhausted or have failed to provide satisfactory benefit, use of intraarticular hyaluronic acid injections may be viewed more favorably than offering no intervention. In the guidelines, no distinction is made between the available intraarticular hyaluronic acid products or between products with various molecular weights.

The Osteoarthritis Research Society International also has guidelines for knee osteoarthritis (2019).¹⁹ These guidelines note that use of intraarticular hyaluronic acid injections are conditionally recommended for patients with knee osteoarthritis. The guidelines comment on the long-term treatment effect with intraarticular hyaluronic acid injections which is associated with symptom improvement beyond 12 weeks and a more favorable safety profile than intraarticular corticosteroid injections.

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. 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.

This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage.

Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles.

Recommended Authorization Criteria

Coverage of hyaluronic acid derivatives is recommended for requests meeting both the preferred product step therapy requirements and indication requirements.

Preferred Product Step Therapy Requirements (New Starts Only)

Criteria. *The patient must meet the following criteria (A or B):*

- A) For patients new to Durolane, Gel-One, Gelsyn-3, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz FX, Sodium hyaluronate injection, Triluron, TriVisc, Visco-3 therapy only,

must have a trial of at least one course of Euflexxa, Synvisc, or Synvisc One prior to approval of Durolane, Gel-One, Gelsyn-3, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz FX, Sodium hyaluronate injection, Triluron, TriVisc, Visco-3. New starts to therapy defined as no use of Durolane, Gel-One, Gelsyn-3, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz FX, Sodium hyaluronate injection, Triluron, TriVisc, Visco-3 within the past 365 days for Medicare patients.

- B)** Patient has a contraindication or other clinical reason why Euflexxa, Synvisc, or Synvisc One cannot be tried before Durolane, Gel-One, Gelsyn-3, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz FX, Sodium hyaluronate injection, Triluron, TriVisc, Visco-3.

Note: Step therapy only required for indications FDA-Approved for both Durolane, Gel-One, Gelsyn-3, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz FX, Sodium hyaluronate injection, Triluron, TriVisc, or Visco-3 and the preferred product(s).

FDA-APPROVED INDICATIONS

1. Osteoarthritis of the Knee.

Criteria. 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 the following criteria (i and ii):

- i.** Diagnosis of the knee to be treated is confirmed by radiologic evidence of knee osteoarthritis; AND

Note: Examples of radiographic evidence includes x-ray, magnetic resonance imaging (MRI), computed tomography (CT) scan, ultrasound.

- ii.** The patient has tried at least TWO of the following three modalities of therapy for osteoarthritis (a, b, c):

a. At least one course of physical therapy for knee osteoarthritis;

b. At least TWO of the following pharmacologic therapies [(1), (2), (3), (4)] **[verification of therapies required]:**

1) Oral or topical nonsteroidal anti-inflammatory drug(s) [NSAID(s)];

Note: Examples of oral NSAIDs include naproxen, ibuprofen, celecoxib. Examples of topical NSAIDs include diclofenac solution or diclofenac gel. Atrial 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 intraarticular corticosteroids to the affected knee; OR

B. Patient has Already Received One or More Courses of a Hyaluronic Acid Derivative in the Same Knee. Approve one repeat course if the patient meets the following criteria (i and ii):

- i.** At least 6 months have elapsed since the last injection with any hyaluronic acid derivative; AND

- ii.** According to the prescriber, the patient had a response to the previous course of hyaluronic acid derivative therapy for osteoarthritis of the knee and now requires additional therapy for osteoarthritis symptoms.

Note: Examples of a response include reduced joint pain, tenderness, or morning stiffness, improved mobility.

Dosing. Approve the following dosing regimens:

- A) **Durolane, Gel-One, Monovisc,:** Approve one injection.
- B) **Hymovisc:** Approve up to two injections given 1 week apart.
- C) **Gelsyn-3, sodium hyaluronate 1% injection, SynoJoynt, 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. **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 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 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
2. **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
3. 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 31, 2020. 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 31, 2020. 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 31, 2020. 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 31, 2020. 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. Trilon [prescribing information]. Florham Park, NJ: Fidia Pharma; March 2019.
15. Trivisc [prescribing information]. Doylestown, PA: OrthogenRx; not dated. Accessed on July 31, 2020. 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 31, 2020. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf/p980044s027d.pdf.
17. Kolasinski SH, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res.* 2019;72(2):149-162.
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. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage.* 2019;27(11):1578-1589.
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.
43. Centers for Medicare and Medicaid Services, National Government Services, Local Coverage Article: Billing and Coding: Hyaluronans Intra-articular Injections of – Related to LCD L33394 (A52420) (Original effective date 10/1/2015; revision effective date 11/7/2019). Accessed on November 25, 2019.
44. Centers for Medicare and Medicaid Services, National Government Services, Inc, Local Coverage Determination (LCD): Drugs and Biologicals, Coverage of, for Label and Off-Label Uses (L33394) [original date 10/01/2015; revision effective date 11/7/2019]. Accessed on November 25, 2019.

Type of Revision	Summary of Changes	Date
Policy created	New Medicare Advantage Medical Policy	07/11/2018
Select revision	Reviewed and revised original policy created 07/11/2018 in accordance with Local Coverage Article A52420.	08/28/2019
Policy revised	Completion of 2019 monthly monitoring process. Removed note indicating that Triluron and Sodium hyaluronate 1% are not referenced in LCA A52420.	10/31/19
Policy revision	Completion of 2019 monthly monitoring process in accordance with Local Coverage Determination L33394, Local Coverage Article A52420.	12/11/2019
Policy revision	Non-clinical update to policy to add the statement “This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does <u>not</u> necessarily mean that the applicable condition or diagnosis is excluded from coverage.”	1/30/2020
Policy revision	*Updated Overview section, added Guidelines section *Added the following note: “Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles.”	4/15/2020
Policy revision	Osteoarthritis of the Knee: Examples of radiographic evidence, non-steroidal anti-inflammatory drugs, and response to therapy were moved to notes in the criteria (previously listed as examples within the criteria). For the criteria applying to patients previously treated who have responded to therapy, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician).	09/18/2020
Selected Revision	SynJoynnt was added to the policy. Criteria for dosing approves for up to three injections given 1 week apart.	07/27/2022