Clinical Policy: Hyaluronate Derivatives

Reference Number: ERX.SPA.175
Effective Date: 01.11.17
Last Review Date: 05.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

The following are hyaluronate derivatives requiring prior authorization: sodium hyaluronate (Euflexxa®, Gelsyn-3™, GenVisc® 850, Hyalgan®, Supartz™, Supartz FX™, Synojoynt™, Triluron™, TriVisc™, VISCO-3™), hyaluronic acid (Durolane®), cross-linked hyaluronate (Gel-One®), hyaluronan (Hymovis®, Orthovisc®, Monovisc®), and hylan polymers A and B (Synvisc®, Synvisc One®).

FDA Approved Indication(s)

Hyaluronate derivatives are indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen) or non-steroidal anti-inflammatory drugs (NSAIDs).

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that hyaluronate derivatives are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Osteoarthritis of the Knee (must meet all)**:**

1. Diagnosis of OA of the knee supported by imaging (e.g., X-ray, MRI);
2. Prescribed by or in consultation with a rheumatologist, orthopedist, or sports medicine physician;
3. Inadequate response to physical therapy as directed by a physical therapist;
4. Failure of ≥ 4 week trial of one of the following (a or b), as evidenced by claims history, unless all are contraindicated or clinically significant adverse effects are experienced:
   a. Oral NSAID at continuous therapeutic (prescription strength) dosing;
   b. Topical NSAID* if member is ≥ 75 years old or unable to take an oral NSAID;
   **Prior authorization may be required for topical NSAIDs*
5. Trial of at least one intra-articular glucocorticoid injection with a documented positive but inadequate response (*see Appendix D for examples*) unless contraindicated or history of intolerance;
   **Prior authorization may be required for intra-articular glucocorticoid injections*
6. Failure of two of the following preferred agents: Durolane, Euflexxa, Gelsyn-3, or Supartz FX, unless clinically significant adverse effects are experienced, all are contraindicated, or request is for one of the aforementioned preferred agents;
7. Member does not have any of the following:
   a. Coexistent active inflammatory arthritis other than OA (e.g., rheumatoid arthritis, spondylitis, gouty arthritis) in the targeted knee;
   b. History of total knee arthroplasty in the targeted knee.

Approval duration: 6 months (one treatment cycle per knee) *(refer to section V)*

B. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Osteoarthritis of the Knee (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by the following, including but not limited to:
   a. Decrease in pain symptoms as evidenced by improvement in the Visual Analog Scale for pain;
   b. Improvement in ambulation or range of motion;
   c. Improvement in stiffness;
   d. Decrease in rescue pain medication use;
3. Member has not had total knee arthroplasty in the targeted knee;
4. Failure of two of the following preferred agents: Durolane, Euflexxa, Gelsyn-3, or Supartz FX, unless clinically significant adverse effects are experienced, all are contraindicated, or request is for one of the aforementioned preferred agents;
5. Six or more months have elapsed since the last treatment cycle.

Approval duration: 6 months (one treatment cycle per knee) (*refer to section V*)

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
NSAIDs: non-steroidal anti-inflammatory drugs
OA: osteoarthritis

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Oral NSAIDs		
diclofenac (Cataflam®, Voltaren®)	50 mg PO BID to TID	150 mg/day
etodolac (Lodine®)	400-500 mg PO BID	1,200 mg/day
fenoprofen (Nalfon®)	400-600 mg PO TID to QID	3,200 mg/day
ibuprofen (Motrin®)	400-800 mg PO TID to QID	3,200 mg/day
indomethacin (Indocin®)	25-50 mg PO BID to TID	200 mg/day
indomethacin SR (Indocin SR®)	75 mg PO QD to BID	150 mg/day
ketoprofen (Orudis®)	25-75 mg PO TID to QID	300 mg/day
meloxicam (Mobic®)	7.5-15 mg PO QD	15 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Oral NSAIDs		
naproxen (Naprosyn®)	250-500 mg PO BID	1,500 mg/day
naproxen sodium (Anaprox®, Anaprox DS®)	275-550 mg PO BID	1,650 mg/day
oxaprozin (Daypro®)	600-1,200 mg PO QD	1,800 mg/day
piroxicam (Feldene®)	10-20 mg PO QD	20 mg/day
salsalate (Disalcid®)	1,500 mg PO BID or 1000 mg PO TID	3,000 mg/day
sulindac (Clinoril®)	150 mg-200 mg PO BID	400 mg/day
tolmetin DS (Tolectin DS®)	400 mg PO TID, titrated up to 1,800 mg QD	1,800 mg/day
Topical NSAIDs		
diclofenac 1.5% (Pennsaid®)	40 drops QID on each painful knee	160 drops/knee/day
Voltaren® Gel 1% (diclofenac)	2-4 g applied to affected area QID	32 g/day
Intra-articular Glucocorticoids		
triamcinolone acetonide (Kenalog®)	40 mg (1 mL) for large joints	80 mg/treatment
Aristospan® (triamcinolone hexacetonide)	10-20 mg for large joints	20 mg/treatment
methylprednisolone acetate (Depo-Medrol®)	20-80 mg for large joints	80 mg/treatment
hydrocortisone acetate	25-50 mg for large joints	75 mg/treatment
Zilretta® (triamcinolone acetonide)	32 mg (5 mL) for large joints	32 mg/treatment

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Durolane, Euflexxa, Gelsyn-3, GenVisc 850, Hyalgan, Supartz, Supartz FX, Synojoynt, Triluron, TriVisc, VISCO-3, Gel-One, Hymovis, Orthovisc, Monovisc, Synvisc, Synvisc One:
    - Known hypersensitivity to hyaluronan preparations
    - Patients with knee joint infections, infections or skin disease in the area of the injection site
  - Hymovis, Monovisc, Orthovisc: known hypersensitivity to gram positive bacterial proteins
  - Monovisc: known systemic bleeding disorders
- Boxed warning(s): none reported

Appendix D: General Information

- Examples of documented positive but inadequate response to intra-articular glucocorticoid injections include but are not limited to the following: inadequate pain relief, frequent need of rescue medications such as NSAIDs or opioids, need to decrease or inability to increase activity levels, adequate pain relief but with steroid-induced hyperglycemia.
- Per the 2014 Osteoarthritis Research Society International guidelines, hyaluronate derivatives are not appropriate for multiple joint OA subtypes or joint OA other than the knee.
  - In DeGroot et al., single hyaluronic acid was compared to saline injection in a small RCT (N=64). At 6 and 12 weeks, there were no significant differences in improvement between the two groups on the American Orthopedic Foot and Ankle Society clinical rating score, the Ankle Osteoarthritis Scale score, or the patient-reported visual analog pain scale. Migliore et al., conducted a review of seven studies for ankle OA that showed mixed results, but were unable to complete a meta-analysis due to use of study design limitations (e.g., inconsistent use of primary endpoints, varying comparators, small sample size) leading to study heterogeneity.

- Richette et al. conducted a multicenter, randomized, placebo-controlled trial in hip OA. At 3 months, hyaluronic acid was not more effective than placebo with a treatment difference in pain score of −0.15 (95% CI −11.04, 10.74). Responder rates were 33.3% for hyaluronic acid and 32.6% for placebo (p = 0.94). Additionally, analgesics were taken by 81% of study days by patients on placebo, and 88% of patients in the hyaluronic acid group.

- There are no studies that have evaluated the efficacy of hyaluronate derivatives in patients with OA and coexistent other inflammatory conditions such as rheumatoid arthritis.
- There is no data to suggest efficacy of hyaluronate derivatives in patients who have had total knee arthroplasty in the targeted knee.

V. Dosage and Administration

Drug Name	Active Ingredient	Dose of Active Ingredient per Injection	Treatment Cycle*
Durolane	Hyaluronic acid	60 mg (3 mL)	1 injection
Euflexxa	Sodium hyaluronate	20 mg (2 mL)	3 injections
Gel One	Cross-linked sodium hyaluronate	30 mg (3 mL)	1 injection
GenVisc 850	Sodium hyaluronate	25 mg (2.5 mL)	3-5 injections
Gelsyn-3	Sodium hyaluronate	16.8 mg (2 mL)	3 injections
Hyalgan	Sodium hyaluronate (Hyalectin®)	20 mg (2 mL)	3-5 injections
Hymovis	Sodium hyaluronate (HYADD®4)	24 mg (3 mL)	2 injections
Monovisc‡	Cross-linked sodium hyaluronate	88 mg (4 mL)	1 injection
Orthovisc‡	Sodium hyaluronate	30 mg (2 mL)	3-4 injections
Supartz FX	Sodium hyaluronate	25 mg (2.5 mL)	3-5 injections
Synojoynt	Sodium hyaluronate	20 mg (2 mL)	3 injections
Synvisc	Cross-linked hylan G-F 20 (hylan A and hylan B polymers)	16 mg (2 mL)	3 injections
Synvisc One	Cross-linked hylan G-F 20 (hylan A and hylan B polymers)	48 mg (6 mL)	1 injection
Triluron	Sodium hyaluronate	20 mg (2 mL)	3 injections
TriVisc	Sodium hyaluronate	25 mg (2.5 mL)	3 injections
VISCO-3	Sodium hyaluronate	25 mg (2.5 mL)	3 injections

**Treatment cycle: Total number of injection per cycle per knee (if treating both knees, double the number of injections per treatment cycle).*
‡Per product label, one injection of Monovisc is equivalent to 3 injections of Orthovisc.

VI. Product Availability

Drug Name	Active Ingredient	Availability**
Durolane	Hyaluronic acid	3 mL syringe
Euflexxa	Sodium hyaluronate	2.25 mL syringe
Gel One	Cross-linked sodium hyaluronate	3 mL syringe
GenVisc 850	Sodium hyaluronate	3 mL syringe
Gelsyn-3	Sodium hyaluronate	2.25 mL syringe
Hyalgan	Sodium hyaluronate (Hyalectin®)	2 mL vial or 2 mL syringe
Hymovis	Sodium hyaluronate (HYADD®4)	5 mL syringe
Monovisc‡	Cross-linked sodium hyaluronate	5 mL syringe
Orthovisc‡	Sodium hyaluronate	3 mL syringe
Supartz FX	Sodium hyaluronate	2.5 mL syringe
Synojoynt	Sodium hyaluronate	3 mL syringe
Synvisc	Cross-linked hylan G-F 20 (hylan A and hylan B polymers)	2.25 mL syringe
Synvisc One	Cross-linked hylan G-F 20 (hylan A and hylan B polymers)	10 mL syringe
Triluron	Sodium hyaluronate	2 mL syringe or 2 mL vial
TriVisc	Sodium hyaluronate	3 mL syringe
VISCO-3	Sodium hyaluronate	2.5 mL syringe

***All syringes/vials are single-use (i.e., one injection/one knee); syringes are pre-filled.*
‡Per product label, one injection of Monovisc is equivalent to 3 injections of Orthovisc.

VII. References

1. Durolane Prescribing Information. Durham, NC: Bioventus LLC; September 2017. Available at https://www.oakneepainrelief.com/durolane/. Accessed August 8, 2020.
2. Euflexxa Prescribing Information. Parsippany, NJ: Ferring Pharmaceuticals, Inc. July 2016. Available at: http://www.euflexxa.com/. Accessed August 8, 2020.
3. Gel-One Prescribing Information. Warsaw, IN: Zimmer; May 2011. Available at: http://www.zimmerbiomet.com/content/dam/zimmer-web/documents/en-US/pdf/medical-professionals/biologics-sports-medicine/Gel-One-Pkg-Insert-Final.pdf. Accessed August 8, 2020.
4. Gelsyn-3 Prescribing Information. Durham, NC: Bioventus LLC; December 2017. Available at: https://www.oakneepainrelief.com/gelsyn_3/. Accessed August 8, 2020.
5. GenVisc 850 Prescribing Information. Doylestown, PA: Orthogen Rx, Inc.; January 2015. Available at: https://genvisc850.com/professionals/assets/info.pdf. Accessed August 9, 2020.
6. Hyalgan Prescribing Information. Parsippany, NJ: Fidia Pharma USA, Inc.; May 2014. Available at: https://hyalgan.com/. Accessed August 9, 2020.
7. Hymovis Prescribing Information. Parsippany, NJ: Fidia Pharma USA, Inc.; October 2015. Available at: http://www.hymovis.com/. Accessed August 9, 2020.
8. Monovisc Prescribing Information. Bedford, MA: Anika Therapeutics, Inc. September 2016. Received from distributor, DePuy Synthes Mitek Sports Medicine, August 10, 2020.
9. Orthovisc Prescribing Information. Woburn, MA: Anika Therapeutics, Inc.; September 2016. Received from distributor, DePuy Synthes Mitek Sports Medicine. Accessed August 10, 2020.
10. Supartz Prescribing Information. Tokyo, Japan: Seigaku Corporation; February 2001. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf/P980044c.pdf. Accessed August 8, 2020.
11. Supartz FX Prescribing Information. Durhan, NC: Bioventus, LLC; April 2015.Available at: http://www.oakneepainrelief.com/wp-content/uploads/2019/09/Supartz_FX_IFU.pdf. Accessed August 8, 2020.
12. Synojoynt Prescribing Information. Gyeonggi-do, Korea: Hanmi Pharm Co., Ltd.; June 2018. Available at: https://www.fda.gov/medical-devices/recently-approved-devices/synojoynttm-p170016. Accessed August 9, 2020.
13. Synvisc Prescribing Information. Ridgefield, NJ: Genzyme Biosurgery; September 2014. Available at: http://products.sanofi.us/synvisc/synvisc.html. Accessed August 9, 2020.
14. Synvisc One Prescribing Information. Ridgefield, NJ: Genzyme Biosurgery; September 2014. Available at: http://products.sanofi.us/synviscone/synviscone.html. Accessed August 8, 2020.
15. Triluron Prescribing Information. Florham Park, NJ: Fidia Pharma; July 2019. Available at: http://triluron.com/wp-content/uploads/2020/06/Leaflet-TRILURON-Medico-USA.pdf . Accessed August 9, 2020.
16. TriVisc Prescribing Information. Doylestown, PA: OrthogenRx, Inc; December 2017. Available at: https://www.trivisc.com/professionals/assets/info.pdf . Accessed August 8, 2020.
17. VISCO-3 Prescribing Information. Warsaw, IN: Zimmer, Inc.; December 2015. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf/p980044s027d.pdf. Accessed August 9, 2020.
18. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at: http://www.clinicalpharmacology-ip.com/.
19. Strand V, Baraf HS, Lavin PT, et al. Effectiveness and safety of a multicenter extension and retreatment trial of Gel-200 in patients with knee osteoarthritis. Cartilage. 2012;3(4):297-304.
20. Sun SF, Hsu CW, Hwang CW, et al. Hyaluronate improves pain, physical function and balance in the geriatric osteoarthritic knee: A 6-month follow-up study using clinical tests. Osteoarthritis Cartilage. 2006;14:696-701.
21. Brown GA. American Academy of Orthopaedic Surgeons clinical practice guidelines: Treatment of osteoarthritis of the knee: Evidence-based guideline, 2nd edition. J Am Acad Orthop Surg. September 2013;21(9):577-9. doi: 10.5435/JAAOS-21-09-577.
22. Kolasinski SL, 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. 2020 Feb;72(2):220-233.

23. Bannuru RR, Osani M, Vaysbrot EE, McAlindon TE. Comparative safety profile of hyaluronic acid products for knee osteoarthritis: a systematic review and network meta-analysis. Osteoarthritis Cartilage. August 2, 2016. pii: S1063-4584(16)30196-0. doi: 10.1016/j.joca.2016.07.010. [Epub ahead of print]
24. Rannou F, Peletier JP, Martel-Pelletier J. Efficacy and safety of topical NSAIDs in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Semin Arthritis Rheum. 2016; 45:S18-S21.
25. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019 Nov;27(11):1578-1589.
26. Nelson AE, Allen KD, Golightly YM, et al. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. Bone and Joint Initiative. Semin Arthritis Rheum. 2014; 43:701-712.
27. Kort NP, Bemelmans YFL, Hugo M, et al. Patient selection criteria for outpatient joint arthroplasty. Knee Surg Sports Traumatol Arthrosec. 2017;25:2668-2675.
28. McGrory BJ, Weber KL, Jevsevar DS, Sevarino K. Surgical management of osteoarthritis of the knee: evidence-based guideline. Journal of the American Academy of Orthopaedic Surgeons 2016; 24(8): e87-e93.
29. DeGroot H, 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 2012; 94(1):2-8.
30. Migliore A, Giovannangeli F, Bizzi E et al. Viscosupplementation in the management of ankle osteoarthritis: a review. Arch Orthop Trauma Surg 2011; 131(1):139-47.
31. 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):824-30.
32. Hayashi D, Roemer FW, Guermazi A. Imaging for osteoarthritis. Ann Phys Rehab Med 2016 Jun;59(3):161-9.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	12.16	01.17
4Q17 Annual Review Converted to new template Added prescriber specialty Removed requirement related to failure of tramadol to avoid promoting opioid use Modified failure of intraarticular glucocorticoid injections to partial response requirement.	09.20.17	11.17
2Q 2018 annual review: modified NSAID trial duration to 4 weeks, added requirement that member must not have coexistent active inflammatory arthritis other than OA or history of total knee arthroplasty in the targeted knee; added Durolane; references reviewed and updated.	01.25.18	05.18
2Q 2019 annual review: added VISCO-3, Supartz, TriVisc; corrected criterion 6 to “and” instead of “or”; references reviewed and updated.	02.05.19	05.19
1Q 2020 annual review: no significant changes; added Synojoynt and Triluron; added redirection to preferred products; moved examples of positive response to therapy from Appendix D to criterion 2 in section IIA; references reviewed and updated.	11.26.19	02.20
4Q 2020 annual review: added sports medicine physician as acceptable specialist; added Appendix D information on response to intra-articular glucocorticoid assessment; references reviewed and updated.	08.10.20	11.20
Revised requirement for diagnosis confirmation by radiologic imaging – generalized to imaging beyond just radiologic type (i.e., to include MRIs); imaging reference added.	12.09.20	02.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Clarified physical therapy should be supervised by a physical therapist, updated hyaluronate product preferencing, and added preferencing to the continued therapy section.	04.13.21	05.21

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.