Clinical Policy: Hyaluronate Derivatives

Reference Number: CP.PHAR.05
Effective Date: 10.01.08
Last Review Date: 02.19 Coding Implications
Line of Business: Commercial, Medicaid, HIM-Medical Benefit 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™, 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.

It is the policy of health plans affiliated with Centene Corporation® 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 radiologic imaging;
2. Prescribed by or in consultation with a rheumatologist or orthopedist;
3. Inadequate response to physical therapy;
4. Failure of a ≥ 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 oral NSAID;
   **Topical NSAID may require prior authorization*
5. Trial of at least one intra-articular glucocorticoid injection with a documented positive but inadequate response unless contraindicated or history of intolerance;
6. Member does not have any of the following (a or b):
   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) (*refer to section V*)

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy (*see Appendix D*);
3. Member has not had total knee arthroplasty in the targeted knee;
4. Six or more months have elapsed since the last treatment cycle.

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

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

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 policies – CP.CPA.09 for commercial and CP.PMN.53 for Medicaid and HIM-Medical Benefit or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
NSAID: non-steroidal anti-inflammatory drug
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 for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Oral NSAIDs		
diclofenac (Voltaren®)	50 mg PO TID	150 mg/day
etodolac (Lodine®)	400-500 mg PO BID	1200 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
fenoprofen (Nalfon®)	400 mg PO TID to QID	3200 mg/day
ibuprofen (Motrin®)	400-800 mg PO TID to QID	3200 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
naproxen (Naprosyn®)	250-500 mg PO BID	1500 mg/day
naproxen sodium (Anaprox®, Anaprox DS®)	275-550 mg PO BID	1650 mg/day
oxaprozin (Daypro®)	600-1200 mg PO BID	1800 mg/day
piroxicam (Feldene®)	10-20 mg PO QD	20 mg/day
salsalate (Disalcid®)	500-750 mg PO TID, titrated up to 3000 mg QD	3000 mg/day
sulindac (Clinoril®)	150 mg-200 mg PO BID	400 mg/day
tolmetin DS (Tolectin DS®)	400 mg PO TID, titrated up to 1800 mg QD	1800 mg/day
Topical NSAIDs		
diclofenac 1.5% (Pennsaid®)	40 drops QID on each painful knee	320 drops/day
Voltaren® Gel 1% (diclofenac)	2-4 g applied to affected area QID	32 g/day
Intra-articular glucocorticoids		
Kenalog® (triamcinolone acetonide)	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

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):
  - Euflexxa, Gelsyn-3, GenVisc 850, Hyalgan, Supartz, Supartz FX, 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
  - Durolane: none reported
  - Hymovis, Monovsic: do not administer to patients with known hypersensitivity to gram positive bacterial proteins
  - Orthovisc: do not administer to patients with known allergies to avian or avian-derived products (including eggs, feathers, or poultry)
  - Mnovisc: do not administer to patients with known systemic bleeding disorders

- Boxed warning(s): none reported

Appendix D: General Information

- Positive response to therapy with hyaluronate derivatives includes decrease in pain symptoms as evidenced by improvement in the Visual Analog Scale for pain, improvement in ambulation or range of motion, improvement in stiffness, and/or decrease in rescue medication use.
- 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

Drug Name	Active Ingredient	Dose of Active Ingredient per Injection	Treatment Cycle*
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
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
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	Sodium hyaluronate	2.5 mL syringe
Supartz FX	Sodium hyaluronate	2.5 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
TriVisc	Sodium hyaluronate	2.5 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

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Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J7320	Hyaluronan or derivative, GenVisc 850, for intra-articular injection, 1 mg
J7321	Hyaluronan or derivative, Hyalgan or Supartz FX or Visco-3, for intra-articular injection, per dose ((Hyalgan dose is 20 mg/2 mL, Supartz and Visco-3 dose is 25 mg/2.5 mL)
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, Gel-Syn, for intra-articular injection, 0.1 mg
C9465	Hyaluronan or derivative, Durolane, for intra-articular injection, per dose

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Removed requirement for enteric coated formulations Added requirement to fail physical therapy, Monovisc and Gel-One to available therapies Changed approval of Gel-One every 13 weeks and other products every 6 months Added need to document interference with ADLs, failure of tramadol Specialist reviewed	01.15	02.15
Removed limit of two injections Converted to bullet points and new template Removed max dosing of APAP and NSAIDs appendix Combined all safety related appendices into one appendix	08.15	10.15
Converted policy to new template. Added two new products approved in 2015: Hymovis and GenVisc850. Approval duration edited to one treatment course every 6 months rather than every 13 weeks. Removed "interference with ADLs" requirement. Edited step therapy to require an inadequate response to all of the following drugs: a two-week trial of oral NSAIDs if <75 years of age or unable to use oral NSAID, topical NSAID for ≥ 2 weeks, tramadol if no opioid abuse or dependence. Removed acetaminophen requirement.	09.16	10.16
Converted to new template. Added Gelsyn-3 to available therapies and prescriber specialty. Modified tramadol requirement to exclude members currently receiving an opioid analgesic Removed requirements related to contraindications and hypersensitivity to hyaluronate preparations (initial) and reasons to discontinue (re-auth) per new safety approach/template update; HCPCS codes added. Specialist reviewed.	04.17	
Tramadol trial removed. Failure of glucocorticoid injections changed to partial response requirement.	08.17	08.17
2Q 2018 annual review: policies combined for commercial and Medicaid lines of business; added HIM-medical benefit; Commercial: modified failure of glucocorticoid injections to partial response requirement; Commercial and Medicaid: 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.	03.06.18	05.18
1Q 2019 annual review: added VISCO-3, Supartz, TriVisc; references reviewed and updated.	10.31.18	02.19

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.