HYALURONIC ACID DERIVATIVES CLINICAL RESOURCE

AGENTS: Hyaluronic Acid Derivatives

- 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)
- Synojoynt (sodium hyaluronate 1%- Arthrex)
- 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)

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OVERVIEW

Euflexxa, Synvisc, Synvisc One are covered without prior authorization.

All other products (Durolane, Gel-One, Gelsyn-3, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz FX, sodium hyaluronate 1%, Synojoynt, Triluron, TriVisc, Visco-3) are not covered. If coverage is requested, a medical necessity review will be completed.

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 is 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 move favorable safety profile than intraarticular corticosteroid injections.

RECOMMENDED GUIDELINES FOR USE (PRIOR AUTHORIZATION IS NOT REQUIRED)

FDA-Approved Indications

1. **Osteoarthritis of the Knee**.):
   - **A)** Initial Therapy. (i, ii, and iii):
     - **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.** Patient has tried at least TWO of the following three modalities of therapy for osteoarthritis (i, ii, iii):
       - **a)** At least one course of physical therapy for knee osteoarthritis;
       - **b)** At least TWO of the following pharmacologic therapies [(1), (2), (3), (4)]
         - **(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. 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 intraarticular 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 One or More Courses of a Hyaluronic Acid Derivative in the Same Knee. (i, ii, and iii):
     - **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; AND
       Note: Examples of a response include reduced joint pain, tenderness, or morning stiffness, improved mobility.
     - **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.
   - **A) Durolane, Gel-One, Monovisc, Synvisc-One:** One injection.
   - **B) Hymovis:** Up to two injections given 1 week apart.
   - **C) Euflexxa, Gelsyn-3, sodium hyaluronate 1% injection, Synojoynt, Synvisc, Triluron, TriVisc, Visco-3:** Up to three injections given 1 week apart.
   - **D) Orthovisc:** up to 4 injections given 1 week apart.
   - **E) GenVisc 850, Hyalgan, Supartz FX:** 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 USE

Hyaluronic acid derivatives are not recommended in the following situations:

1. **Acute Ankle Sprain.** A randomized, controlled, prospective trial was conducted which assessed the use of intraarticular hyaluronic acid in acute ankle sprains.[20-21] Patients treated with intraarticular hyaluronic acid (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 intraarticular hyaluronic acid 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 intraarticular hyaluronic acid 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 intraarticular hyaluronic acid and potential for harm, the guidelines for the management of hand, hip, and knee OA by American College of Rheumatology (2019) do not recommend use of hyaluronic acid derivatives in patients with hand or hip OA.[17] Small trials have also investigated intraarticular hyaluronic acid in other joints, including ankle OA and hip OA.[23-38] More data are needed to determine if there is a role for intraarticular hyaluronic acid for the treatment of OA involving other joints. A small trial (n = 70) found that intraarticular hyaluronic acid did not result in increased benefit for adhesive capsulitis of the shoulder (also known as frozen shoulder) in patients who were already receiving physical therapy.[39] Another small study (n = 159) did not show benefit of intraarticular hyaluronic acid over corticosteroid or placebo injections in patients with subacromial impingement.[40]

3. **Pathologic Conditions of the Knee Other than Osteoarthritis** (e.g., chondromalacia patellae, osteochondritis dissecans, patellofemoral syndrome, post-anterior cruciate ligament [ACL] reconstruction). Intraarticular hyaluronic acid derivatives are indicated in knee osteoarthritis.[1-16] Adequate, well-designed trials have not clearly established the use of these products in other conditions of the knee.[41-42]

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