



## INLAND EMPIRE HEALTH PLAN

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee.

**Drug:** Synvisc, Synvisc-One (hylan GF20); Euflexxa, Hyalgan, Orthovisc, Supartz (Sodium hyaluronate)

**Class:** Hyaluronans

**Formulary medication:** Acetaminophen, ibuprofen, naproxen

**Effective Date:** September 2004, updated January 2006, August 2008, August 2009

### **Policy/Criteria:**

Hyaluronans may be medically necessary if the following criteria are met:

- Documented symptomatic osteoarthritis of the knee.
- Trial of at least 3 months of conservative therapies (at least 3 different analgesic including acetaminophen, and non-steroidal anti-inflammatory (NSAID), or the patient is unable to tolerate drug therapy because of adverse side effects.

### Authorization for retreatment:

1. Patient shows significant improvements in function and reduced pain from the injection;
2. Documented reduction in dose of NSAIDs or analgesics during the 6 month period following the last injection in the previous series and, six months or longer has elapsed since the last injection in the previous series.
3. At least 6 months since the last injection. Remission of symptoms after the second treatment cycle may need further orthopedic specialists' evaluation.

### **Clinical Justification:**

1. Hyaluronans have shown efficacy in reduction in pain and improvement in functional capacity in some patients.
2. The reduction in pain and improvement persist for up to six months.
3. Hyaluronan treatment seems to be optimally used early in the disease process- for patients who have mild to moderate osteoarthritis as demonstrated by clinical examination and radiographically confirmed by a Kellgren-Lawrence grade of 2 or 3. Patients who have severe disease would likely benefit more from reconstructive knee surgery than from hyaluronan therapy, based on the studies which showed better outcomes in patients with early stage or intermediate stage disease.<sup>4</sup>
4. The safety of repeat treatment cycles is not clinically established due to the limited clinical experience with the compound.
5. According to the Orthopedic Surgeons Consensus Conference, for patients who are satisfied with the functional improvements and pain relief characteristic of intra-articular hyaluronan therapy, retreatment is recommended in approximately 6 months following the initial treatment cycle, or when the patient experiences pain.<sup>6</sup> One of the studies examined the patients who

received five courses (every 6 months) of five weekly injections over 2 years. The analysis showed that symptomatic improvements without acceleration of joint damage after retreatment were particularly likely in patients with early stage osteoarthritis. Pain decreased and joint flexion and extension increased progressively during the course of the trial.<sup>4</sup>

6. One other similar study evaluated the patients who received 3 weekly injections of sodium hyaluronate every 3 months for a year, and it suggested that hyaluronate may delay structural progression of the disease.<sup>7</sup>
7. Cochrane review conducted by Bellamy et al. (2006), assessed the effects of viscosupplementation in treatment of OA of the knee. Selection criteria included all RCTs for hyaluronans and hylan derivatives. Sixty three trials met criteria. The authors concluded that viscosupplementation was effective compared to placebo for OA. The authors also noted the lack of head to head data to determine the relative efficacy of the different products compared to each other. <sup>8</sup>
8. In a double blind randomized control trial conducted in 2006, Euflexxa was shown to be non-inferior to Synvisc at 12 weeks (N = 321). The adverse effects were similar with the most common AE being injection site pain.<sup>9</sup>
9. One prospective active controlled trial (n=392) comparing Synvisc vs. Hyalgan measuring the reduction in pain based on 10 cm visual analog scale was conducted by Raman et al. in 2008. The results indicated that at 12 weeks, there was no statistical difference between Synvisc and Hyalgan in terms of pain reduction. At 24 weeks, Synvisc showed statistical superiority compared to Hyalgan (49.3% vs. 10.6%) in improvement from baseline pain. Both medications showed significant improvement compared to baseline. An important limitation to note for this study was the fact that it was not blinded and there is potential for biased reporting. <sup>10</sup>
10. The Medical Letter determined that intra-articular injections with HA has shown some benefit compared to placebo. It is also noted comparative trials are lacking. No one HA is determined to be superior and is generally treated as a class effect. <sup>11</sup>
11. The American College of Rheumatology in their recommendations for the medical management osteoarthritis of the hip and knee (2000) determined that although the different preparations of hyalyronic acid exists based on molecular weight, to date no differences in clinical efficacy has been demonstrated. <sup>12</sup>

#### Reference:

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2. Kolarz G, Kotz R, Hochmayer I. Long-term benefits and repeated treatment cycles of intra-articular sodium hyaluronate (Hyalgan) in patients with osteoarthritis of the knee. *Semin Arthritis Rheum.* 2003 Apr;32(5):310-9.
3. Kotz R, Kolarz G. Intra-articular hyaluronic acid: duration of effect and results of repeated treatment cycles. *Am J Orthop.* 1999; 28(Suppl 11):5-7.
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6. Osteoarthritis and Beyond: A Consensus on the Past, Present, and Future of Hyaluronans in Orthopedics. 2002 Orthopedic Surgeon Consensus Conference. <http://www.orthobluejournal.com/CMEarticles/art049.asp>
7. Barrett JP, Siviero P. Retrospective study of outcomes in Hyalgan-treated patients with osteoarthritis of the knee. *Clin Drug Invest.* 2002; 22:87-97.
8. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev.* 2006;(2):CD005321.

9. Kirchner M, Marshall D. A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage*. 2006;14(2):154-162.
10. Raman R, et al. Efficacy of Hylan G-F 20 and Sodium Hyaluronate in the treatment of osteoarthritis of the knee — A prospective randomized clinical trial, *The Knee* (2008), doi:10.1016/j.knee.2008.02.012
11. *The Medical Letter*. Intra-articular Injections for Osteoarthritis of the Knee. Vol 48. Mar 27, 2006.
12. American College of Rheumatology. Recommendations for the medical management of osteoarthritis of the hip and knee. Vol 43. No. 9. Sep 2000. PP. 1905-1915

#### Update: Cost of Treatment

Brand	Generic	Dosing	Cost
Euflexxa	1% Sodium Hyaluronate	2 ml injected intra-articularly into affected knee at weekly intervals for 3 weeks (total of 3 injections)	(1) Each Injection = \$206.06 (3) Injections = \$618.18
Hyalgan	1% Sodium Hyaluronate	2 ml injected intra-articularly into affected knee at weekly intervals for 3-5 weeks (total of 3-5 injections)	(1) Each Injection = \$145.78 (3) Injections = \$437.34 (5) Injections = \$728.90
Orthovisc	1% Sodium Hyaluronate	2 ml injected intra-articularly into affected knee at weekly intervals for 3-4 weeks (total of 3-4 injections)	(1) Each Injection = \$270.00 (3) Injections = \$810.00 (4) Injections = \$1080
Synvisc	Hylan G-F 20	2 ml injected intra-articularly into affected knee at weekly intervals for 3 weeks (total of 3 injections)	(1) Each Injection = \$563.20 (3) Injections = \$1689.00
Synvisc-One	Hylan G-F 20	Single articular injection (1 syringe has 3 doses in it)	(1) Each Injection = \$844.80
Supartz	1% sodium hyaluronate	2 ml injected intra-articularly into affected knee at weekly intervals for 3-5 weeks (total of 3-5 injections)	(1) Each Injection = \$162.50 (3) Injections = \$487.50 (5) Injections = \$812.50

#### Cost Per Treatment (3) Injections only:

Synvisc > Synvisc-One > Orthovisc\* > Euflexxa > Supartz\* > Hyalgan\*

\*Hyalgan, Orthovisc, and Supartz have shown contradicting efficacy at (3) doses compared to placebo in various trials. These drugs have high potential for dosage creep

**Recommendation:** Euflexxa appears to provide a consistent cost savings compared to other preparations, all available data indicates a class effect across all products.