



Policy Title:	Hyaluronic acid Intra-articular Injection Policy: Durolane, Euflexxa, Gel-One, Gelsyn, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz/Supartz FX, Synjoynt, Synvisc, Synvisc-One, Triluron, Trivisc, &Visco-3		
		Department:	PHA
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Purpose: To support safe, effective, and appropriate use of Hyaluronic acid Intra-articular Injections.

Scope: Medicaid*, Commercial, Medicare-Medicaid Plan (MMP)

*(Medication only available on the Medical Benefit)

Policy Statement:

Hyaluronic acid Intra-articular Injections are covered under the Medical Benefit when used within the following guidelines. Use outside of these guidelines may result in non-payment unless approved under an exception process. Euflexxa is the preferred Hyaluronic acid Intra-articular Injection.

Procedure:

Coverage of Hyaluronic acid Intra-articular Injections will be reviewed prospectively via the prior authorization process based on criteria below.

Initial Criteria:

- Documented symptomatic osteoarthritis of the knee; AND
- Trial and failure of conservative therapy including physical therapy, pharmacotherapy [e.g., non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen (up to 1 g 4 times/day) and/or topical capsaicin cream] has been attempted and has not resulted in functional improvement after at least 3 months; AND
- The patient has failed to adequately respond to aspiration and injection of intra-articular steroids; AND
- The patient reports pain which interferes with functional activities (e.g., ambulation, prolonged standing); AND
- There are no contraindications to the injections (e.g., active joint infection, bleeding disorder); AND
- Requests for non-Euflexxa Hyaluronic acid intra-articular injections require that a patient must have a documented failure, intolerance or contraindication to Euflexxa; OR



- MMP members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements

Continuation of Therapy Criteria:

- Meets all initial criteria; **AND**
- Disease response with treatment as defined by improvement in signs and symptoms of pain and a stabilization or improvement in functional capacity during the 6-month period following the previous series of injections as evidenced by objective measures; **AND**
- Absence of unacceptable toxicity from the previous injections. Examples of unacceptable toxicity include: severe joint swelling and pain, severe infections, anaphylactic or anaphylactoid reactions, etc.

Coverage durations: one series per knee for 6 months

Per §§ 42 CFR 422.101, this clinical medical policy only applies to INTEGRITY in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD).

Policy Rationale:

Durolane, Euflexxa, Gel-One, Gelsyn, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz/Supartz FX, Synjoynt, Synvisc, Synvisc-One, Triluron, Trivisc, and Visco-3 were reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Durolane, Euflexxa, Gel-One, Gelsyn, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz/Supartz FX, Synjoynt, Synvisc, Synvisc-One, Triluron, Trivisc, & Visco-3 according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For INTEGRITY (Medicare-Medicaid Plan) members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.

Billable Units (per dose and over time):

<i>DRUG</i>	<i>HCPCS</i>	<i>1 Billable Unit (BU)</i>	<i>BU per administration</i>	<i>Number of Administrations per knee per 180 days</i>
Euflexxa	J7323	1 dose	1	3
Durolane	J7318	1mg	60	1
Gel-One	J7326	1 dose	1	1



GelSyn-3	J7328	0.1 mg	168	3
Gen-Visc 850	J7320	1 mg	25	5
Hyalgan; Supartz; Supartz FX	J7321	1 dose	1	5
Hymovis	J7322	1 mg	24	2
Monovisc	J7327	1 dose	1	1
Orthovisc	J7324	1 dose	1	4
Synvisc	J7325	1 mg	16	3
Synvisc-One	J7325	1 mg	48	1
Visco-3	J7321	1 dose	1	3
Synojynt	J7331	1 mg	20	3
Trivisc	J7329	1mg	25	3
Triluron	J7332	1 mg	20	3

Investigational Use: All therapies are considered investigational when used at a dose or for a condition other than those that are recognized as medically accepted indications as defined in any one of the following standard reference compendia: American Hospital Formulary Service Drug Information (AHFS-DI), Thomson Micromedex DrugDex, Clinical Pharmacology, Wolters Kluwer Lexi-Drugs, or Peer-reviewed published medical literature indicating that sufficient evidence exists to support use. Neighborhood does not provide coverage for drugs when used for investigational purposes.

Applicable Codes:

Below is a list of billing codes applicable for covered treatment options. The below tables are provided for reference purposes and may not be all-inclusive. Requests received with codes from tables below do not guarantee coverage. Requests must meet all criteria provided in the procedure section.

The following HCPCS/CPT codes are:

HCPCS/CPT Code	Description
J7320	Genvisc
J7321	Hyalgan or Supartz or Visco-3
J7322	Hymovis
J7323	Euflexxa
J7324	Orthovisc
J7325	Synvisc/Synvisc-One
J7326	Gel-One

J7327	Monovisc
J7331	Synjoynt
J7332	Triluron
J7328	Gel-Syn-3
J7329	Trivisc
J7318	Durolane

Summary of Evidence:

Durolane: Durloane is a clear, transparent, gel of highly purified hyaluronate that is used for the treatment of pain in osteoarthritis of the knee in patients who have failed to response to non-pharmacological approaches or simple analgesics. The original randomized, controlled clinical studies of Durolane, 35GA0001, 35GA0301, and 35GA0608 were used to evaluate the outcome measure associated with a pain responder rate, 40% reduction from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores and an absolute reduction of at least 5 points in that score. Neither of the first two superiority trials were evaluated against saline, showed superiority over saline. Study TG1018DLN was a prospective, randomized, controlled, multicenter clinical study with 349 patients intended to demonstrate that Durolane was non-inferior to a commercially-available, 5-injection regimen HA product in the treatment of pain associated with knee osteoarthritis (OA) over 26 week. The primary outcome measure was based on the WOMAC 20-point Likert-scale with an 8% margin. Patients were followed for 26 weeks. Effectiveness was assessed at Weeks 6, 10, 14, 18, and 26. Safety was assessed at screening and at Weeks 0, 1, 2, 3, 4, 6, 10, 14, 18, and 26. The results demonstrated that Durolane was non-inferior to the 5-injection HA. Common adverse events include Baker's cyst, phlebitis, injection site reactions, and arthropathy.

Euflexxa: Euflexxa is a viscoelastic, sterile solution of highly purified, high molecular weight hylauronan used in the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics. A prospective, randomized, double-blind, active control study was conducted with 321 patients in Germany to assess the safety and efficacy of Euflexxa for 12 weeks. For this trial, the main performance analysis for determining non-inferiority was determined using the improvement in the average of the five patient's self-evaluation pain parameters measured by the VAS WOMAC index at Week 12 from baseline. The results indicate that the effect of Euflexxa on pain relief was not inferior to that of a commercially available hyaluronan. Another study involving 588 patients with knee pain due to osteoarthritis was conducted in the United States. The pain scores were used to compare the effectiveness of Euflexxa to saline injection: Patients were asked to rate how pain was felt on the 100 mm scale after 50 foot walk at 1, 2, 3, 6, 12, 18 and 26 weeks. Euflexxa group improved 25.7 mm from the baseline pain score, whereas the saline group improved 18.5 mm. There was more improvement in Euflexxa group than the saline group. Study results showed



significant improvement in osteoarthritis knee pain relief with Euflexxa therapy lasting up to 6 months. The study also showed that a repeated cycle of Euflexxa for an additional 26 weeks (1 year total) was safe. Common adverse reactions include arthralgia, musculoskeletal pain, back pain, and joint swelling.

Gel-One: Gel-One is a sterile, transparent, and viscoelastic hydrogel composed of cross-linked hyaluronate used in the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics. A total of 379 patients were enrolled in a prospective, randomized and double-blind controlled study to assess the safety and effectiveness of a single injection of Gel-One. Patients reported pain with symptomatic OA of the knee defined by WOMAC VAS Pain sub score of ≥ 40 mm in the study knee and ≤ 20 mm in the contralateral knee. The study primary endpoint, WOMAC Pain sub score at Week 13, demonstrated that Gel-One® was superior to PBS with a 6.39 mm advantage at Week 13 in the ITT population of the SI 6606/01 study ($p = 0.0374$). Common adverse events include joint swelling, arthritis, injection site reactions and gait disturbance.

Gelsyn: Gelsyn is a sterile, buffered solution of highly purified sodium hyaluronate used in the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics. The safety and efficacy of Gel-Syn was assessed in a prospective, randomized, double-blind, active control (commercial hyaluronan), non-inferiority study conducted at 23 centers in Europe with 380 patients. The primary efficacy variable for this study was the Western Ontario McMaster Universities (WOMAC) pain sub score at week 26 which was required to meet a delta of 8 mm. Overall WOMAC pain sub score mean reduction from baseline was 30.8 mm (56%) for the Gel-Syn treatment group, in contrast to 29.4 mm (53%) for patients receiving commercial hyaluronan. The most common adverse reaction is injection site pain.

GenVisc 850: GenVisc 850 is a sterile, viscoelastic non-pyrogenic solution of hyaluronate 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 simple analgesics. The Yong Ping study was a parallel-controlled, randomized, multi-center clinical conducted to evaluate the comparative efficacy and safety of GenVisc 850 intra-articular injections for the treatment of degenerative osteoarthritis knee pain to Supartz/Supartz FX in 229 subjects. In the full analysis set (FAS) population, the VAS pain on movement of the Supartz/Supartz FX group at week 6 decreased by 48.0 ± 23.39 mm compared to baseline, and that of the GenVisc 850 group decreased by 49.2 ± 21.50 mm. The difference between the two groups was not statistically or clinically significant ($P > 0.05$). Common adverse events include injection site pain, arthralgia, bleeding and arthritis.

Hyalgan: Hyalgan is a viscous, high molecule weight solution used in the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics. A multicenter prospective, three-phased, clinical trial was investigated in 495 patients to assess the safety and efficacy of Hyalgan. Efficacy was measured with three primary effectiveness criteria; measurement of pain during a 50-foot walk test using a 100mm Visual Analog Scale, a categorical assessment of pain by a masked evaluator, and



another categorical assessment evaluated by the subject. At week 26, in the 100mm VAS walk, the difference between the Hyalgan treated group and placebo group adjusted means was 8.85 ($p=0.0043$). For both categorical assessments, the Hyalgan treated patients experienced less than the placebo treated patients. The improvement in pain on the VAS by the Hyalgan treated group were at least 50% benefit. Common adverse events include injection site reactions, local skin reactions, pruritis, and GI complaints.

Hymovis: Hymovis is a sterile, non-pyrogenic, viscoelastic hydrogel 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 simple analgesics. Hymovis was studied in a randomized, double-blind, saline-controlled study to evaluate the safety and effectiveness in 529 patients. The primary endpoint was to determine the superiority of Hymovis compared to saline by evaluating the Western Ontario and McMaster Universities Osteoarthritis Index absolute improvement from baseline at Week 26. The pain reduction from baseline for HYMOVIS® was -19.47 mm on the whole 100 mm WOMAC A Pain scale and that of saline placebo was -18.13 mm. The primary effectiveness endpoint was not met in this study. As shown below in Table 6, the study did not demonstrate a statistically significant difference, as well as a clinically meaningful difference of at least 6 mm, between the two groups in WOMAC A Pain Scores at six months. At -6.0 mm on a 100mm WOMAC VAS scale, which is considered by Agency a valid clinically important difference, the CDF plots demonstrate that Hymovis demonstrates a higher degree of clinical improvement than Hyalgan for all significant test endpoints. Common adverse events include bursitis, injection site reactions, arthrosis and phlebitis.

Monovisc: Monovisc is a sterile, non-pyrogenic, viscoelastic solution of hyaluronan 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 simple analgesics. The Monovisc 0702 study was a randomized, double-blinded, saline-controlled study conducted under IDE at 31 centers in the U.S. and Canada to evaluate the safety and effectiveness of a single injection of Monovisc in 369 patients with symptomatic osteoarthritis of the knee. The primary endpoint was to determine the superiority of Monovisc compared to saline by evaluating the proportion of patients achieving $\geq 40\%$ relative improvement and ≥ 15 mm absolute improvement from baseline in the WOMAC VAS Pain Score (100mm scale) through Week 12. In the 0702 study, Monovisc did not demonstrate superiority over saline for the primary effectiveness endpoint of patients with $\geq 40\%$ relative improvement from baseline and ≥ 15 mm absolute improvement from baseline in the WOMAC VAS Pain Score through Week 12 ($p=0.145$). Common adverse events include arthralgia, joint swelling and injection site reactions.

Orthovisc: Orthovisc is a sterile, non-pyrogenic, clear, viscoelastic solution of hyaluronan 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 simple analgesics. The effectiveness of Orthovisc for the treatment of osteoarthritis of the knee was evaluated in three main studies; two randomized, controlled, double-blind multicenter studies (OAKO5O1 and OAK2001) that involved unilateral treatment, and one study (OAK9801) that involved bilateral treatment. For the



effectiveness subgroup population, the primary effectiveness analysis performed was to determine the proportion of patients achieving a 20% improvement from baseline in the WOMAC Pain Score in conjunction with a minimum absolute improvement of 50mm from baseline in the WOMAC Pain Score, and a 40%, and 50% improvement from baseline in WOMAC Pain Score at four assessment points between Weeks 7/8 to 21/22 for the index knee. The primary effectiveness analysis was performed to determine the proportion of patients achieving a 20% improvement from baseline in the WOMAC Pain Score in conjunction with a minimum absolute improvement of 50 mm from baseline in the WOMAC Pain Score, and a 40% and 50% improvement from baseline in WOMAC Pain Score at four assessment points between Weeks 8 to 22 for the index knee. Common adverse events include arthralgia, headache and injection site reactions.

Supartz: Supartz is 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 simple analgesics. The safety and effectiveness of Supartz FX was based on an integrated analysis of five randomized, multi-center, blinded, "placebo controlled" clinical trials. The Lequesne Index, although a primary measure of effectiveness in only three studies (France, Germany, and Sweden) was common to all five studies. It was used for the integrated analysis of effectiveness across all five studies. The primary measure used in the other two studies was the WOMAC Index in Australia, and VAS pain ratings in the United Kingdom. The difference in reduction in total Lequesne scores between the SUPARTZ FX treated group and the control group is 0.68, which is statistically significant in the integrated analysis ($p=0.0026$). Additionally, the Australian study shows a significant difference between Supartz FX and control in both the WOMAC pain ($p=0.045$) and stiffness ($p=0.024$) scores and Lequesne total scores ($p=0.0114$). Common adverse events include arthralgia, arthropathy and back pain.

Synjoynt: Synjoynt is a sterile, non-pyrogenic, clear, viscoelastic solution of hyaluronan 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 simple analgesics. The safety and effectiveness of Synjoynt was evaluated in a double-blind, prospective, multi-site, randomized, three-arm, parallel group, pivotal trial in adult subjects. The primary effectiveness endpoint was the change from Baseline in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain score in the target knee at Week 26. At the Week 26 visit the LS mean (standard deviation [SD]) change from Baseline in WOMAC pain scores were $-132 \text{ mm} \pm 128 \text{ mm}$ in the placebo group versus $-168 \text{ mm} \pm 129 \text{ mm}$ in the Synjoynt group (Table 6, Figure 1). At the Week 26 visit the difference (placebo versus Synjoynt) in LS mean change from Baseline in WOMAC pain score was significantly greater for the Synjoynt group versus the placebo group [36 mm (95% CI: 10.25; 62.11)] demonstrating the superiority of Synjoynt to placebo. Common adverse events include joint reactions, infection and phlebitis.

Synvisc: Synvisc is 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 simple analgesics. The safety and effectiveness of Synvisc were evaluated in three clinical trials involving patients aged 40 and older, including 136 women and 81 men. The first study, conducted at four



sites in Germany, was a randomized, double-blind trial comparing Synvisc with saline in 103 subjects over 26 weeks. Synvisc showed significantly greater improvement in all measures compared to saline. The second study, also in Germany, involved 29 subjects and had similar results, with the most pain relief occurring 8-12 weeks after treatment. The third study, conducted at five U.S. sites, compared Synvisc with arthrocentesis in 90 subjects over four weeks. Both groups improved significantly, but there were no significant differences between them. Covariate analyses revealed no factors significantly affecting the results. Common adverse events include arthralgia, arthritis and gait disturbance.

Synvisc-One: Synvisc-One is 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 simple analgesics. The study was a prospective, multi-center, randomized, double-blind, two-arm (parallel group) clinical study conducted at 21 sites. The double-blind, saline-controlled study demonstrated that a single injection of 6 mL of Synvisc-One is effective in providing symptomatic relief up to 26 weeks in patients with primary knee OA. There was a statistically significant estimated treatment difference (-0.15, $p=0.047$) between the Synvisc-One treatment group and the saline control for the primary efficacy endpoint of this study, being the change from baseline over the course of the 26-week study using the patient's assessment of his/her pain. Common adverse events include arthralgia, arthropathy and joint effusion.

Triluron: Triluron is 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 simple analgesics. To specifically compare the effectiveness of Triluron (investigational device) to Hyalgan (control device), a retrospective comparison of data prospectively collected from two randomized, controlled trials was performed. The primary endpoint analysis was mean change in WOMAC Pain from baseline and used baseline observation carried forward to replace missing data. The mean change in WOMAC Pain from baseline at 6 months post-injections were -18.4 and -14.9 in the Triluron and Hyalgan, respectively. The difference between the means was -3.545 and the upper limit of the one-sided 95% CI (0.2403), which was less than the upper limit of 9. Thus, the primary effectiveness evaluation demonstrates that Trilurin is non-inferior to Hyalgan. Common adverse events include arthralgia, and infection.

Trivisc: Trivisc is 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 simple analgesics. The primary clinical performance testing for TriVisc, as per the FDA Modernization Act (1997), was based on data from a clinical study under PMA supplement P980044/S27. This study aimed to establish the safety and effectiveness of three weekly intra-articular injections of the Visco supplement for treating knee osteoarthritis pain in patients unresponsive to conservative therapies. Conducted in the U.S. under IDE G130271, the study was a pivotal, multi-center, randomized, double-blind, parallel arm, active-controlled, and non-inferiority trial. It compared TriVisc to a commercially available hyaluronan. The primary objective was to demonstrate non-inferiority in pain relief, measured by the WOMAC VAS pain subscale over 12 weeks. The study included 384 evaluable patients, showing that TriVisc was non-inferior to the control, with a 52.5% average



reduction in pain at week 12. Common adverse events include bleeding, arthritis, and injection site pain.

Visco-3: Visco-3 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 simple analgesics. The safety and effectiveness of Visco-3 was studied in a pivotal, 12-week, multi-center, randomized, double-blind, parallel arm, active controlled, non-inferiority study. The primary objective of the study was to demonstrate non-inferiority of Visco-3 group to the active control group for the relief of knee joint pain in subjects with OA of the knee as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) visual analog scale (VAS) (0-100 mm) pain subscale score change from baseline (CFB) over Week 3, Week 6, and Week 12 in the per-protocol set. A comparative clinical trial of Visco-3 to a commercially available hyaluronan successfully demonstrated non-inferiority within an 8% margin as determined by comparisons of the change from baseline (CFB) of WOMAC VAS pain subscale scores over the 12 week duration of the trial. Common adverse events include aggravated osteoarthritis, arthrosis and bursitis.

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