Hyaluronic Acid Derivatives

Policy Number: MC/PC 018
Effective Date: May 1, 2025

Instructions for Use

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Related Policies

- n/a

Coverage Rationale

<Please refer to Medical Benefit Plan Sponsor for preferred medications. Preferred products may be updated and therefore subject to change>.

Osteoarthritis (OA) of the knee

For initial coverage of hyaluronic acid derivative products for Osteoarthritis (OA) of the knee, the following will be required:

- Diagnosis of osteoarthritis of the knee **and**
- Trial and failure, contraindication, or intolerance to two of the following:
  - Acetaminophen
  - Duloxetine
  - Non-steroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen)
  - Topical capsaicin
  - Tramadol **and**
- Trial and failure, contraindication, or intolerance to intra-articular steroid injection (e.g., methylprednisolone, triamcinolone

For reauthorization coverage of hyaluronic acid derivative products, the following will be required:

- Documentation of improvement in pain with previous course of treatment **and**
- At least 6 months have elapsed since last injection of the prior treatment cycle

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan

document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J7318	Hyaluronan or derivative, Durolane, for intra-articular injection, 1 mg
J7320	Hyaluronan or derivative, GenVisc 850, for intra-articular injection, 1 mg
J7321	Hyaluronan or derivative, Hyalgan, Supartz or Visco-3, for intra-articular injection, per dose
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, Gelsyn-3, for intra-articular injection, 0.1 mg
J7329	Hyaluronan or derivative, Trivisc, for intra-articular injection, 1 mg
J7331	Hyaluronan or derivative, Synojoynt, for intra-articular injection, 1 mg
J7332	Hyaluronan or derivative, Triluron, for intra-articular injection, 1 mg

ICD-10 Code	Description
M13.0	Polyarthritis, unspecified
M17.0	Bilateral primary osteoarthritis of knee
M17.10	Unilateral primary osteoarthritis, unspecified knee
M17.11	Unilateral primary osteoarthritis, right knee
M17.12	Unilateral primary osteoarthritis, left knee
M17.2	Bilateral post-traumatic osteoarthritis of knee
M17.30	Unilateral post-traumatic osteoarthritis, unspecified knee
M17.31	Unilateral post-traumatic osteoarthritis, right knee
M17.32	Unilateral post-traumatic osteoarthritis, left knee
M17.4	Other bilateral secondary osteoarthritis of knee
M17.5	Other unilateral secondary osteoarthritis of knee
M17.9	Osteoarthritis of knee, unspecified

Background

Osteoarthritis (OA) is the most common form of joint disease, affecting over 30 million adults in the United States (U.S.) (Centers for Disease Control and Prevention [CDC] 2024). It is characterized by breakdown of the cartilage, hypertrophic changes in the bone, deterioration of tendons and ligaments, and various degrees of inflammation of the synovium (American College of Rheumatology [ACR] 2024).

The management of OA includes nonpharmacologic therapies (eg, exercise, knee brace, and weight management), pharmacologic therapies (eg, oral, topical, and intra-articular medications), and surgical interventions (eg, total joint

arthroplasty). Management should be individualized and take into consideration various factors such as the severity of the patient's disease, occupational needs, and comorbid medical conditions (Kolasinski 2020, Medical Letter 2020).

Intra-articular hyaluronic acid (HA) preparations, also referred to as viscosupplementation, are claimed to improve the diminished viscoelasticity of synovial fluid and possibly prevent degradation of articular cartilage (Medical Letter 2020).

Clinical Evidence

Strand et al, *J Pain Res.* 2015;8:217-228.

Study Objective: To assess the safety and efficacy of U.S.-approved intra-articular HA products for symptomatic knee OA.	
Study Design, Follow-up	**Treatment Groups**

• Systematic review and meta-analysis of 29 saline-controlled, RCTs (N = 4866)	• Intra-articular HA (n = 2673)
	  ○ The most commonly studied viscosupplements were Hyalgan (18 studies), Synvisc (9), Supartz/Supartz FX/Artzal [not marketed in the U.S., but identical to Supartz/Supartz FX] (6), Orthovisc (3), Gel-One (1), and Euflexxa (1).
	  ○ The total number of injections received by patients ranged from 1 to 5, with the exception of 1 study in which patients received 3 cycles of 3 injections.
	• PBS control (n = 2193)

Inclusion Criteria	**Exclusion Criteria**
• Randomized, sham-controlled study design • Primary diagnosis of knee OA • Identical treatment and follow-up conditions between intra-articular HA and sham-control groups • At least 1 extractable efficacy or safety outcome • Study evaluates a U.S.-approved HA product	• Concomitant interventional therapies
Primary Endpoints	
• Knee pain severity and function at 4 to 13 weeks and at 14 to 26 weeks	

- **Results:**
  - Comparing the results of intra-articular HA injection to pretreatment values, the standardized mean difference (SMD) for knee pain was 1.37 (95% CI, 1.12 to 1.61) at 4 to 13 weeks and 1.14 (95% CI, 0.89 to 1.39) at 14 to 26 weeks (both $p < 0.001$). For knee function, the SMDs were 1.16 (95% CI, 0.99 to 1.34) and 1.07 (95% CI, 0.84 to 1.30), respectively (both $p < 0.001$).
    - There was high heterogeneity (I^2 = 74% to 92%, all $p < 0.001$) for all treatment effects, with evidence of publication bias for knee pain, but not knee function.
  - Compared to controls, the SMD for knee pain was 0.43 (95% CI, 0.26 to 0.60) at 4 to 13 weeks and 0.38 (95% CI, 0.21 to 0.55) at 14 to 26 weeks (both $p < 0.001$). Knee function SMD was 0.34 (95% CI, 0.16 to 0.51) and 0.32 (95% CI, 0.18 to 0.45), respectively, at the same time intervals (both $p < 0.001$).
    - Heterogeneity among studies was high for knee pain (I^2 = 73% to 75%, both $p < 0.001$) and moderate for knee function (I^2 = 54% to 69%, both $p < 0.01$). Publication bias was evident for

both knee pain treatment effects and for knee function at 4 to 13 weeks, but not for knee function at 14 to 26 weeks.
    - There were no statistically significant risk differences between intra-articular HA and controls for any safety outcome, with absolute risk differences of 0.7% (95% CI, -0.2 to 1.5%) for SAEs, 0% (95% CI, -0.4 to 0.4%) for treatment-related SAEs, 0% (95% CI, -1.6 to 1.6%) for patient withdrawal, and 0.2% (95% CI, -0.4 to 0.8%) for AE-related patient withdrawal.
        - There was minimal heterogeneity in safety outcomes among studies (all $I^2 = 0\%$) with no evidence of publication bias for any safety outcome.
- **Authors' conclusion:**
    - Intra-articular injection of U.S.-approved viscosupplements is safe and efficacious through 26 weeks in patients with symptomatic knee OA.
- **Study sponsorship:**
    - This study was funded by the HA Viscosupplement Coalition (Bioventus LLC, Durham, NC, USA; DePuy Synthes Mitek Sports Medicine, Raynham, MA, USA; Ferring Pharmaceuticals Inc., Parsippany, NJ, USA; Fidia Pharma USA, Inc., Parsippany, NJ, USA; Zimmer, Inc., Warsaw, IN, USA).
- **Study limitations:**
    - Efficacy outcomes were inconsistent across studies and influenced by study design factors and publication bias.
    - Due to sample size considerations, the authors did not attempt to analyze treatment effects by viscosupplement type or molecular weight.
    - Most studies excluded patients with end-stage (K-L grade 4 or equivalent) knee OA; therefore, the efficacy of intra-articular HA cannot be determined in this population.

Bannuru et al, *Osteoarthritis Cartilage*. 2011;19(6):611-619.

Study Objective: To evaluate the therapeutic trajectory of intra-articular HA vs placebo for knee OA.	
Study Design, Follow-up	**Treatment Groups**
• Meta-analysis of 54 randomized trials (N = 7545)	• HA • Placebo
Inclusion Criteria	**Exclusion Criteria**
• Randomized trials comparing intra-articular HA vs placebo to treat knee OA • Trials must have reported extractable outcome data for at least 1 measure of pain or function or stiffness, as recommended for OA clinical trials. When an article provided data on more than 1 pain scale, the outcome highest on the hierarchy was extracted. o Pain: ▪ WOMAC OA Index Pain Subscale (VAS or Likert) ▪ Index joint pain when walking (VAS or Likert) ▪ Index joint pain during activities other than walking (VAS or Likert) ▪ Spontaneous index joint pain (VAS or Likert) o Function	• N/A

▪ WOMAC OA Index Function Subscale (VAS or Likert version) ▪ Function score for index joint (VAS or Likert scale). ○ Stiffness: ▪ WOMAC OA Index Stiffness Subscale (VAS or Likert version) ▪ Stiffness score for index joint (VAS or Likert scale).	
Primary Endpoints	**Secondary Endpoints**
• Pain reduction at specified time points: 2 weeks (1-2 weeks), 4 weeks (3-6 weeks), 8 weeks (7-10 weeks), 12 weeks (11-14 weeks), 16 weeks (15-18 weeks), 20 weeks (19-22 weeks) and 24 weeks (23-26 weeks) ○ The authors considered an effect size above 0.20 to be clinically relevant.	• Function and stiffness at 8 or 12 weeks or at the end of the trial, whichever appeared first

- **Results:**
  - A total of 49 trials contributed to the meta-analysis of pain-related outcomes (n = 6962); 16 trials (n = 2571) contributed to the meta-analysis of function-related outcomes; and 15 trials (n = 2488) contributed to the meta-analysis of stiffness-related outcomes.
  - For the primary outcome measure, the effect size favored HA by week 4 (0.31; 95% CI, 0.17 to 0.45), reaching a peak at week 8 (0.46; 95% CI, 0.28 to 0.65), and then trending downwards with a residual detectable effect at week 24 (0.21; 95% CI, 0.10 to 0.31). The heterogeneity score (I^2) for overall effect size for pain was 70%.
    - This therapeutic trajectory was consistent among the subset of high quality trials (2570 participants) and on multivariate analysis adjusting for correlation between time points.
  - The paucity of data at each time point precluded evaluation of the therapeutic trajectory for joint function and stiffness.
    - The effect size for joint function was 0.31 (95% CI, 0.11 to 0.51) with an I^2 score of 79%, indicating high heterogeneity among the trials. The pooled effect size of the 5 high quality trials (n = 1536 participants) was 0.12 (95% CI, -0.04 to 0.27), showing no effect, and the I^2 score was 51%.
    - The effect size for joint stiffness was 0.31 (95% CI, 0.12 to 0.49) favoring HA, with an I^2 score of 74%. The pooled effect size of the 4 high quality trials (n = 1283) was 0.10 (95% CI, 0.11 to 0.31), showing no effect, and the I^2 score was 67%.
- **Authors' conclusion:**
  - It is inferred from the meta-analysis that intra-articular HA is efficacious by 4 weeks, reaches its peak effectiveness at 8 weeks and exerts a residual detectable effect at 24 weeks. The peak effect size (0.46; 95% CI, 0.28 to 0.65) is greater than published effects from other OA analgesics (APAP [effect size = 0.13; 95% CI, 0.04 to 0.22]; NSAIDs [effect size = 0.29; 95% CI, 0.22 to 0.35]; COX-2 inhibitors [effect size = 0.44; 95% CI, 0.33 to 0.55]).
- **Study sponsorship:**
  - This study was supported by the Agency for Healthcare Research and Quality (AHRQ) and by the National Center for Research Resources.
- **Study limitations:**
  - Trial characteristics including study quality, sample size and power calculations, duration of the trial, use of ITT analysis, losses to follow-up, and industry involvement, varied substantially.

- Not all of the trials provided data for each of the time points.
- The meta-analysis pooled several HA agents which differ in characteristics.
- The placebo effect sizes in OA trials tend to be large and aspiration of synovial fluid may contribute to a response in patients receiving placebo.

Medina et al. *J Fam Pract.* 2006;55(8):669-675.

Study Objective: To evaluate the effect of intra-articular HA injection on pain, stiffness, and disability in patients with knee OA.	
Study Design, Follow-up	**Treatment Groups**
• Meta-analysis of 7 randomized trials	• HA (eg, Hyalgan and Synvisc) • Placebo (saline)
Inclusion Criteria	**Exclusion Criteria**
• Randomized clinical trials evaluating HA injection for OA of the knee vs placebo • Trials using the WOMAC or Lequesne indexes as outcome measurements and providing means and SDs	• N/A
Primary Endpoints	
• WOMAC or Lequesne indexes	

- **Results:**
  - The analysis for the outcome measurements on the WOMAC scale revealed no significant difference between groups in regard to pain (95% CI, -0.6043 to 5.4755) or disability (95% CI, -0.8282 to 4.8619) (CIs that cross the 0-value represent a non-significant difference between active treatment and control). The outcome measurement for stiffness demonstrated a significant difference between treatment and control (95% CI, 2.1780 to 8.7955).
  - The analysis for the outcome measurement on the Lequesne index revealed a significant difference between groups for measurements taken up to 6 months post-treatment (95% CI, 1.2315 to 2.6268). However, these differences were not seen in the 6+ month outcomes analysis (95% CI, -0.8489 to 0.04787).
- **Authors' conclusion:**
  - HA injection may provide short-term relief of pain and improved functionality for patients with OA of the knee, but benefits do not last beyond 6 months. There is no sufficient reason to recommend or not recommend HA injection for treatment of OA of the knee.
- **Study sponsorship:**
  - No sources of financial support declared.

Modawal et al, *J Fam Pract*. 2005;54(9):758-767.

Study Objective: To evaluate the efficacy of intra-articular viscosupplementation therapy with HA for pain relief of knee OA.	
Study Design, Follow-up	**Treatment Groups**
• Meta-analysis of 11 DB, PC, RCTs	• HA (hyaluronan and hylan G-F 20) ○ Nine trials evaluated hyaluronan and 2 trials evaluated hylan G-F 20. • Placebo
Inclusion Criteria	**Exclusion Criteria**
• DB, PC, RCTs of HA for the treatment of knee OA • Trials measuring pain using a 100-mm VAS	• Reviews, meta-analyses, comparison trials, and trials reporting VAS as part of the WOMAC scale
Primary Endpoints	

- Summary estimate of difference in change of VAS pain at 1 week, 5 to 7 weeks, 8 to 12 weeks, and 15 to 22 weeks after the last HA injection

- **Results:**
  - Eleven trials contributed to the calculation of the summary estimate of difference in change of VAS pain at 1 week; 6 trials contributed to the estimate between 5 to 7 weeks and 8 to 12 weeks; and only 3 trials contributed to the estimate at 15 to 22 weeks.
  - At week 1, the mean difference in pain scores between treatment and placebo was 4.4 (95% CI, 1.1 to 7.2). However, the value was -1.0 (95% CI, -3.2 to 1.2) for the analysis restricted to the 7 good quality trials.
  - At weeks 5 to 7, the mean difference in pain scores was 17.6 (95% CI, 7.5 to 28.0). The value was 7.2 (95% CI, 2.4 to 12.0) for the analysis restricted to the 2 good quality studies.
  - At weeks 8 to 12, the mean difference in pain scores was 18.1 (95% CI, 6.3 to 29.9). The value was 7.1 (95% CI, 3.0 to 11.3) for the analysis restricted to good quality trials.
  - At weeks 15 to 22, the mean difference was 4.4 (95% CI, -15.3 to 24.1). All 3 studies were of good quality.
  - High heterogeneity was observed at all time intervals except week 1.
  - Clinical trials using hylan GF-20 showed statistically significant better results than those using hyaluronan at weeks 5 to 7 and 8 to 12.
- **Authors' conclusion:**
  - Intra-articular viscosupplementation was moderately effective in relieving knee pain in patients with OA at 5 to 7 and 8 to 12 weeks after the last injection but not at 15 to 22 weeks.
- **Study sponsorship:**
  - No sources of financial support declared.
- **Study limitations:**
  - Because only 3 trials assessed patients after 12 weeks, the sample size was too small to definitively rule out a significant therapeutic benefit after 12 weeks.
  - Although the meta-regression analysis suggested that hylan GF-20 was more effective than hyaluronan at 5 to 12 weeks, the number of clinical trials was relatively small and both of the hylan G-F 20 studies were of poor quality. Thus, the authors could not conclude that one form is better than the other.
  - Some of the studies allowed analgesics such as NSAIDs and APAP, which may have altered the response to HA treatment.
  - An ITT analysis was only performed in 2 studies; the treatment effects may have been smaller had the other trials used an ITT analysis.

<u>Intra-articular HA agents vs placebo and other HA preparations</u>

Newberry et al, Agency for Healthcare Research and Quality (US); 2015.

- The AHRQ conducted a systematic review to evaluate the effectiveness of intra-articular HA to improve quality of life (QoL) and to delay or prevent the need for total knee replacement (TKR) in subjects ≥ 65 years of age with OA of the knee.
  - Three RCTs and 13 observational studies reported on TKR after administration of intra-articular HA injections. Two RCTs did not specify TKR as a pre-specified outcome of interest, but as a treatment failure. Only 1 RCT assessed TKR as a pre-specified outcome of interest and it found that intra-articular HA resulted in a non-statistically significantly longer delay of TKR compared to placebo.
  - Eighteen RCTs that enrolled participants of average age 65 or older reported on functional outcomes of intra-articular HA injection. Pooled analysis of 10 sham-injection PC, assessor-blinded trials showed an SMD of -0.23 (95% CI, -0.34 to -0.02) significantly favoring HA at 6 months' follow-up.
    - Durability of effect could not be assessed because of the short duration of most studies.
    - Too few head-to-head trials were available to assess superiority of one product over another.

- Three RCTs that compared changes in QoL between HA- and placebo-treated participants reported no differences between active treatment and placebo.
- Two recent large, good quality systematic reviews that conducted meta-analysis of the effects of HA on pain and function (pooling 71 and 52 RCTs for the outcome of pain) showed a significant and clinically important effect of HA on both outcomes among adults of all ages, but a subgroup analysis that included only the largest DB, PC studies reduced the average effect of HA to less than the pre-specified MCID.
- Studies of intra-articular HA reported few SAEs, with no statistically significant difference in the rates of serious or non-serious AEs between HA- and placebo-treated groups.
- Authors' conclusion: Trials enrolling older participants show a small, statistically significant effect of HA on function and relatively few SAEs; however no studies limited participation to those 65 years or older. No conclusions can be drawn from the available literature on delay or avoidance of TKR through the use of HA. Studies that can compare large numbers of treated and untreated individuals, preferably with a randomized design, are needed to answer this question.

Altman et al, *Am J Sports Med*. 2016;44(8):2158-2165.

- A meta-analysis of 68 RCTs was conducted to determine whether there are differences in efficacy and safety with respect to intrinsic properties (eg, derivation of the HA, size of the HA) of available intra-articular HA injections for knee OA. The primary outcome measure was the mean pain score at the reported follow-up nearest to 26 weeks after injection.
  - High molecular weight products (≥ 3000 kDa) had an effect size of -0.52 (95% CI, -0.56 to 0.48). Low molecular weight products (≤ 1500 kDa) had a pooled effect size of -0.18 (95% CI, -0.19 to -0.17), while moderate molecular weight (< 3000 and > 1500 kDa) products had an effect size of -0.31 (95% CI, -0.42 to -0.2).
    - The pooled effect sizes were analyzed by use of an MCID of 0.37.
  - Subgroup analysis pertaining to flare-ups at the injection site found a statistically significant difference between treatments derived from bacterial processes and avian-derived molecules (3.04% [95% CI, 2.34% to 3.95%] vs 13.19% [12.04% to 14.44%], respectively; p ≤ 0.001).
  - The pooled incidence of injection site flare-up was 13.73% (95% CI, 12.33% to 15.27%) for high molecular weight products, 3.31% (95% CI, 2.04% to 5.30%) for moderate molecular weight products, and 10.73% (95% CI, 9.27% to 12.39%) for low molecular weight products. Statistical significance was demonstrated between products with high vs moderate molecular weight (p ≤ 0.001), moderate vs low molecular weight (p ≤ 0.001), and high vs low molecular weight (p = 0.007), with respect to injection site flare-up.
  - A statistically significant difference was found between the pooled low molecular weight and high molecular weight results for discontinuation due to treatment-related AE data (2.20% [95% CI, 1.70% to 2.84%] vs 0.77% [95% CI, 0.48% vs 1.21%], p = 0.004).
  - Bacteria-derived/naturally produced HA demonstrated a discontinuation rate of 1.49% (95% CI, 1.05% to 2.12%), while avian-derived HA demonstrated a discontinuation rate of 1.00% (95% CI, 0.73% to 1.37%) (p = 0.09).
  - Subgroup analysis of trials that reported data about effusion after injection did not demonstrate statistically significant differences based on product molecular weight (1.75% to 1.90%).
  - Statistical significance was demonstrated between bacteria-derived/naturally produced HA and avian-derived-HA with respect to the incidence of effusion (0.54% [95% CI, 0.26% to 1.12%] vs 3.44% [95% CI, 2.77% to 4.27%], respectively; p ≤ 0.001).
  - Authors' conclusion: Despite similarities, intra-articular HA products should not be treated as a group, as there are differences in intra-articular HA products that influence both efficacy and safety. In the available literature, intra-articular HA products with a molecular weight ≥ 3000 kDa and those derived from biological fermentation relate to superior efficacy and safety-factors that may influence selection an intra-articular HA product for OA of the knee.
  - Study sponsorship:
    - This study was funded by Ferring Pharmaceuticals.

- Study limitations:
  - There was heterogeneity in the trial designs and in the quality of reporting within the included trials. The incomplete or unclear reporting of pain, efficacy, and/or safety data made it difficult to systematically pool results. Safety data were often unreported.

Bellamy et al, *Cochrane Database Syst Rev*. 2006;(2):CD005321.

Study Objective: To assess the effects of viscosupplementation in the treatment of OA of the knee.	
Study Design, Follow-up	**Treatment Groups**
• Systematic (Cochrane) review of 76 RCTs	• Viscosupplements ○ The review included HA products of widely different molecular weights and formulations (eg, Euflexxa, GenVisc 850, Supartz/Supartz FX, Hyalgan, Synvisc, and Orthovisc) • Control treatments: placebo (saline, arthrocentesis) and active treatment (eg, NSAIDs, physical therapy)
Inclusion Criteria	**Exclusion Criteria**

• Single-blinded or DB, PC or comparative, RCTs using 1 or more viscosupplements for the treatment of OA of the knee
• At least 1 of the first 3 OMERACT III outcome measures had to be reported:
  ○ Pain
  ○ Physical function
  ○ Patient global assessment
  ○ Joint imaging (for studies of 1 year or longer)
	• N/A

Primary Endpoints	

• Outcome measures included pain, physical function, patient global assessment, and joint function
  ○ Continuous outcome measures were analyzed as WMD with 95% CI; where different scales were used to measure the same outcome, SMD was used.
  ○ Dichotomous outcomes were analyzed by RR.	

- **Results:** (only the data for products currently available in the U.S. are reported below)
  - The pooled analyses of the effects of viscosupplements vs placebo controls generally supported the efficacy of these products. In these analyses, differential efficacy effects were observed for different products on different variables and at different time points (refer to the results for individual products below). In general, the 5 to 13 week post-injection period showed a percent improvement from baseline of 28 to54% for pain and 9 to32% for function.
  - In general, comparable efficacy was noted against NSAIDs and longer-term benefits were noted in comparisons against intra-articular corticosteroids (refer to the results for individual products below).
  - In general, few AEs were reported in the HA trials included in these analyses.
  - Product: Adant (a.k.a. GenVisc 850 [available in the U.S.])
    - One small RCT comparing Adant to Hyalgan found no statistically significant differences between the 2 groups with respect to patient global assessment at 1 to 4 weeks, 5 to 13 weeks, and 14 to 26 weeks, or with respect to the risk of experiencing injection-related pain.
  - Product: Artz (a.k.a. Artzal, Supartz/Supartz FX [available in the U.S.])
    - In comparative studies of Artz vs placebo, several outcome measures (Lequesne index, range of motion, WOMAC OA Index) failed to detect a statistically significant difference with the exception of patient global assessment at 1 to 4 weeks and 5 to 13 weeks and pain and the

number of clinical failures at 5 to 13 weeks post-injection. Overall, the data generally supported the efficacy and safety of Artz.
        - In comparative analyses of Artz and Hylan G-F 20, there were no statistically significant differences in any of the efficacy or safety variables.
    - Product: BioHy (a.k.a. Arthrease, Euflexxa [available in the U.S.], Nuflexxa)
        - The PC study was inconclusive for efficacy, likely as a result of methodological issues. There were no between-group differences in the proportion of patients experiencing post-injection pain and in overall withdrawals and there were no systemic reactions in either group.
        - In the comparative analyses of BioHy and Hylan G-F 20, the pre-specified criteria for non-inferiority were met. Joint effusion was significantly less likely in the BioHy group and statistically significant differences in favor of BioHy were detected for WOMAC function and number of patients using rescue analgesics at 1 to 4 and 5 to 13 weeks, but not in other efficacy variables including pain. The 2 products could not be differentiated based on this single study.
    - Product: Hyalgan
        - In comparative studies of Hyalgan vs placebo, statistically significant differences were found at 1 to 4 weeks (eg, pain on weight-bearing, spontaneous pain, pain at rest, Lequesne index), at 5 to 13 weeks (eg, pain on weight-bearing, spontaneous pain, pain at rest, Lequesne index), and at 14 to 26 weeks (eg, pain on weight-bearing, WOMAC pain). Overall, the data generally supported the efficacy and safety of Hyalgan.
        - The comparative studies of Hyalgan vs corticosteroids supported the efficacy and safety of Hyalgan, with some 5 to 13 week advantages in favor of Hyalgan over methylprednisolone.
        - The comparative study of Hyalgan vs NSAIDs suggested that both treatments were comparable in efficacy and safety, with the exception of more injection-site pain and fewer GI events with Hyalgan.
    - Product: Hylan G-F 20 (Synvisc)
        - In comparative studies of Hylan G-F 20 vs placebo, statistically significant differences were found at 1 to 4 weeks (eg, WOMAC OA Index pain/stiffness/physical function, pain on weight-bearing, pain at rest), at 5 to 13 weeks (eg, WOMAC OA Index pain/stiffness/physical function, pain on weight-bearing, pain at rest, Lequesne index), and at 14 to 26 weeks (eg, WOMAC OA Index pain/function, pain on weight-bearing). Overall, the data generally supported the efficacy and safety of Hylan G-F 20.
        - The comparative studies of Hylan G-F 20 vs corticosteroids suggested that Hylan G-F 20 was comparable in efficacy to intra-articular corticosteroids, but with a slower onset and a longer duration of action. There were no statistically significant differences between groups in the majority of safety variables.
        - The comparative studies of Hylan G-F 20 vs NSAIDs suggested that both treatments were comparable in efficacy and that Hylan G-F 20 was similar or slightly superior in safety.
    - Product: Orthovisc
        - Comparative studies of Orthovisc vs placebo found statistically significant differences in WOMAC pain and function at 1 to 4 weeks, 5 to 13 weeks, and 14 to 26 weeks post-injection; WOMAC stiffness at 5 to 13 weeks and 14 to 26 weeks; and patient global assessment at 1 to 4 weeks and 5 to 13 weeks. These analyses supported the efficacy and safety of Orthovisc.
        - Comparative studies of Orthovisc vs corticosteroids suggested that Orthovisc was comparable in efficacy to intra-articular corticosteroids at 1 to 4 weeks and superior at 5 to 13 weeks and at 14 to 26 weeks, with Orthovisc having a slower onset and a longer duration of action. There were no statistically significant differences between the groups with regard to safety profile.
- **Authors' conclusion:**
    - Viscosupplementation is an effective treatment for OA of the knee with beneficial effects on pain, function, and patient global assessment; and at different post-injection periods but especially at the 5 to 13 week post-injection period. The magnitude of the clinical effect, as expressed by the WMD and SMD, is different for different products, comparisons, time points, variables and trial designs. There are few

randomized head-to-head comparisons of different viscosupplements; thus, caution is advised in drawing conclusions regarding the relative value of different products. The clinical effect for some products vs placebo, on some variables at some time points, is in the moderate to large effect-size range.
    - In general, sample-size restrictions preclude any definitive comment on the safety of the HA class of products; however, within the constraints of the trial designs, no major safety issues were detected. In some analyses, viscosupplements were comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic AEs.
    - In some analyses, HA products had more prolonged effects than intra-articular corticosteroids.
    - Overall, the analyses support the use of HA products in the treatment of knee OA.
- **Study sponsorship:**
    - This study was supported by the Centre of National Research on Disability and Rehabilitation Medicine (CONROD), Australia.
- **Study limitations:**
    - There was a lack of standard outcome measures, restricting pooling of data.
    - Open trials, case series, and studies that did not meet inclusion criteria were omitted.

Intra-articular HA agents vs pharmacologic interventions

Jevsevar et al, *J Am Acad Orthop Surg*. 2018;26(9):325-336.

- A network meta-analysis of 56 RCTs was conducted to determine the efficacy of NSAIDs, APAP, intra-articular corticosteroids, intra-articular platelet-rich plasma, and intra-articular HA compared with each other as well as with placebo (oral and intra-articular) for treatment of knee OA.
    - For pain, all active treatments showed significance over oral placebo. Only intra-articular corticosteroids showed significance over intra-articular placebo.
    - For function, no intra-articular treatments showed significance compared with either placebo, and naproxen was the only treatment showing significance compared with oral placebo.
    - The 5 treatments with the highest probability of ranking 1 to 5 (1 being most effective) when evaluating pain reduction were intra-articular corticosteroids, ibuprofen, intra-articular platelet-rich plasma, naproxen, and celecoxib. Intra-articular HA ranked sixth.
    - The 5 treatments with the highest probability of ranking 1 to 5 when evaluating functional improvement were naproxen, diclofenac, celecoxib, ibuprofen, and intra-articular platelet-rich plasma. Intra-articular HA ranked 7th after intra-articular corticosteroids.
    - When evaluating both pain reduction and functional improvement, the top 1 to 5 ranking treatments were naproxen, intra-articular corticosteroids, intra-articular platelet-rich plasma, ibuprofen, and celecoxib. Intra-articular HA ranked 7th after diclofenac.
    - Authors' conclusion: Naproxen ranked as the most effective among conservative treatments of knee OA and should be considered when treating pain and function because of its relative safety and low cost. The best available evidence was analyzed, but there were instances of inconsistency in the design and duration among articles, potentially affecting uniform data inclusion.
    - Sponsorship:
        - No sources of financial support declared.

Bannuru et el, *Ann Intern Med*. 2015;162(1):46-54.

Study Objective: To compare the relative efficacy of available treatments for knee OA.	
Study Design, Follow-up	**Treatment Groups**
• Network meta-analysis of 137 RCTs (N = 33,243) ○ A total of 129 trials (n = 32,129) contributed to the analyses of pain-related outcomes; 76 trials (n =	• APAP (n = 1877) • Diclofenac (n = 940) • Ibuprofen (n = 1317) • Naproxen (n = 3283) • Celecoxib (n = 7579)

24,059) contributed to the analyses of physical function outcomes; and 55 trials (n = 18,267) contributed to the analyses of stiffness outcomes.	• Intra-articular HA (n = 4806) • Intra-articular corticosteroids (n = 967) • Intra-articular placebo (n = 3664) • Oral placebo (n = 7696)
Inclusion Criteria	**Exclusion Criteria**
• RCTs in humans with clinical or radiologic diagnosis of symptomatic primary knee OA that compared at least 2 interventions of interest • Study reported extractable data for at least 1 measure of pain, function, or stiffness	• N/A
Primary Endpoint	
• SMDs were calculated for pain, function, and stiffness at 3-month follow-up	

- **Results:**

  Pain
  - All interventions were statistically significantly better than oral placebo, with effect sizes ranging from 0.18 (95% credible interval [CrI], 0.04 to 0.33) for the least efficacious treatment (APAP) to 0.63 (95% CrI, 0.39 to 0.88) for the most efficacious treatment (intra-articular HA).
  - All treatments except APAP met the prespecified criteria for clinically significant improvement.
  - Naproxen, ibuprofen, diclofenac, intra-articular HA, and intra-articular corticosteroids were statistically significantly superior to APAP, with effect sizes ranging from 0.20 (95% CrI, 0.03 to 0.37) for naproxen to 0.45 (95% CrI, 0.18 to 0.72) for intra-articular HA.
  - Intra-articular HA and intra-articular corticosteroids were statistically significantly superior to intra-articular placebo, with effect sizes of 0.34 (95% CrI, 0.26 to 0.42) and 0.32 (95% CrI, 0.16 to 0.47), respectively.
  - Intra-articular HA was statistically significantly superior to celecoxib and naproxen, with effect sizes of 0.30 (95% CrI, 0.04 to 0.55) and 0.25 (95% CrI, 0.01 to 0.49), respectively.
  - Intra-articular placebo was statistically significantly better than oral placebo (effect size, 0.29 [95% CrI, 0.04 to 0.54]).
  - Intra-articular treatments were more effective than oral treatments.

  Function
  - All interventions except intra-articular corticosteroids were statistically significantly superior to oral placebo, with effect sizes ranging from 0.15 to 0.45.
  - Naproxen, ibuprofen, diclofenac, and celecoxib were statistically significantly better than APAP.
  - Intra-articular HA was statistically significantly better than intra-articular placebo and intra-articular corticosteroids.
  - Intra-articular placebo was not significantly better than oral placebo (effect size, 0.15 [CrI, -0.22 to 0.53]).

  Stiffness
  - Naproxen, ibuprofen, diclofenac, and celecoxib were statistically significantly better than oral placebo and APAP.
  - Intra-articular HA was statistically significantly better than intra-articular placebo.
  - Intra-articular placebo was not significantly better than oral placebo (effect size, 0.10 [CrI, -0.26 to 0.46]).

  Safety
  - In general, oral NSAIDs led to more GI AEs and withdrawals due to AEs than oral placebo and APAP.
  - Withdrawals due to AEs were more common with oral treatments than intra-articular therapies.

    - The most commonly reported AEs among the intra-articular therapies were transient local reactions, such as pain, swelling, and arthralgia, which usually subsided in a few days. These events were reported to be similar between different intra-articular therapies (corticosteroids and HA).
- **Authors' conclusion:**
    - Intra-articular treatments were superior to NSAIDs, possibly because of the integrated intra-articular placebo effect. Small but robust differences were observed between active treatments. All treatments except APAP showed clinically significant improvement from baseline pain.
- **Study sponsorship:**
    - AHRQ
- **Study limitations:**
    - There were few head-to-head comparisons.
    - There was a lack of long-term data.
    - There was inadequate reporting of safety data.

Clinical Guidelines

- American College of Rheumatology/Arthritis Foundation – Guideline for the management of OA of the hand, hip, and knee (Kolasinski et al 2020) are Conditionally Against Intra-articular HA.
    - The benefit of intra-articular HA was restricted to the studies with higher risk of bias: when limited to trials with low risk of bias, meta-analysis has shown that the effect size of HA injections compared to saline injections approaches zero.
    - The finding that best evidence fails to establish a benefit, and that harm may be associated with these injections, motivated the recommendation against use of this treatment.
    - Many providers want the option of using HA injections when glucocorticoid injections or other interventions fail to adequately control local joint symptoms. In clinical practice, the choice to use HA injections in the knee OA patient who has had an inadequate response to nonpharmacologic therapies, topical and oral NSAIDs, and intra-articular steroids may be viewed more favorably than offering no intervention, particularly given the impact of the contextual effects of intra-articular HA injections.
    - The conditional recommendation against is consistent with the use of HA injections, in the context of shared decision-making that recognizes the limited evidence of benefit of this treatment, when other alternatives have been exhausted or failed to provide satisfactory benefit.

- OA Research Society International (OARSI) – Guidelines for the non-surgical management of knee, hip, and polyarticular OA (Bannuru et al 2019) Recommendations for knee OA:
    - The use of intra-articular corticosteroids and HA are conditionally recommended in individuals with knee OA in all groups (ie, no comorbidities, GI, CV, frailty, widespread pain/depression) (Recommendation level: 1B for GI, CV, frailty; 2 for no comorbitidies, widespread pain/depression).
    - Good clinical practice statements: Intra-articular corticosteroids are conditionally recommended for acute and short-term pain relief. Intra-articular HA is conditionally recommended for longer-term treatment effect, as it is associated with symptom improvement beyond 12 weeks and demonstrated a favorable safety profile.

- Department of Veterans Affairs/Department of Defense (VA/DoD): Practice guideline for the non-surgical management of hip & knee OA (2020)
    - Recommend offering topical non-steroidal anti-inflammatory drugs for patients with pain associated with osteoarthritis of the knee. (Strong for).
    - There is insufficient evidence to recommend for or against the use of topical non-steroidal anti-inflammatory drugs for patients with pain associated with osteoarthritis of the hip (Neither for nor against).
    - Suggest offering topical capsaicin for patients with pain associated with osteoarthritis of the knee. (Weak for)

- There is insufficient evidence to recommend for or against the use of topical capsaicin for patients with pain associated with osteoarthritis of the hip. (Neither for nor against)
- Suggest offering acetaminophen and/or oral nonsteroidal anti-inflammatory drugs for pain associated with osteoarthritis of the hip and knee. (Weak for)
- Suggest offering duloxetine as an alternative or adjunctive therapy for patients with an inadequate response or contraindications to acetaminophen or non-steroidal anti-inflammatory drugs for pain associated with osteoarthritis of the knee. (Weak for)
- Suggest against initiating opioids (including tramadol) for pain associated with osteoarthritis of the hip and knee. For patients already on long-term opioid therapy, refer to the current VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. (Weak against)
- Suggest offering an intra-articular corticosteroid injection for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions. (Weak for)
- Suggest offering an intra-articular, image-guided corticosteroid injection for patients with persistent pain due to osteoarthritis of the hip inadequately relieved by other interventions. (Weak for)
- Suggest offering intra-articular viscosupplementation injection(s) for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions. (Weak for)
- Suggest against the use of intra-articular viscosupplementation injection(s) of the hip. (Weak against)

- American Academy of Orthopaedic Surgeons (AAOS) – Treatment of OA of the knee (Brophy et al 2022)
  - Oral NSAIDs are recommended to improve pain and function in the treatment of knee osteoarthritis when not contraindicated. (Strength of recommendation: Strong).
  - Oral acetaminophen is recommended to improve pain and function in the treatment of knee osteoarthritis when not contraindicated. (Strength of recommendation: Strong).
  - Oral narcotics, including tramadol, result in a significant increase of adverse events and are not effective at improving pain or function for treatment of osteoarthritis of the knee. (Strength of recommendation: Strong).
  - Hyaluronic acid intra-articular injection(s) is not recommended for routine use in the treatment of symptomatic osteoarthritis of the knee. (Strength of recommendation: Moderate).
  - Intra-articular (IA) corticosteroids could provide short-term relief for patients with symptomatic osteoarthritis of the knee. (Strength of recommendation: Moderate).

- American Medical Society for Sports Medicine (AMSSM): Position statement concerning viscosupplementation injections for knee OA: Importance for individual patient outcomes (Trojian et al 2016)
  - The AMSSM recommends the use of HA for the appropriate patients with knee OA. Using The Grades of Recommendation, Assessment, Development and Evaluation Working Group system, there are multiple RCTs indicating high quality evidence.
  - The AMSSM recommends viscosupplementation injections for K-L grade 2-3 knee OA in those patients above the age of 60 years based on high quality evidence demonstrating benefit using OMERACT-OARSI Responder Rating.
  - The AMSSM suggests viscosupplementation injections for knee OA for those under the age of 60 years based on moderate quality evidence due to response of treatment in those over 60 years of age.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

DUROLANE is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacological therapy or simple analgesics, e.g. acetaminophen.

EUFLEXXA 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 (e.g., acetaminophen).

Gel-One is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to non-pharmacologic therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), or simple analgesics, e.g., acetaminophen.

GELSYN-3 is indicated for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g. acetaminophen).

GenVisc 850 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, e.g., acetaminophen.

HYALGAN 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, e.g., acetaminophen.

HYMOVIS 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 or simple analgesics (e.g., acetaminophen).

MONOVISC 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 or simple analgesics (e.g., acetaminophen).

ORTHOVISC is indicated in the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and to simple analgesics, e.g. acetaminophen.

SUPARTZ/SUPARTZ FX is indicated for treatment of pain in osteoarthritis (osteoarthritis) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, e.g., acetaminophen.

SYNOJOYNT 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 (e.g., acetaminophen).

SYNVISC/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 nonpharmacologic therapy and simple analgesics, e.g., acetaminophen.

TRILURON is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy, and to simple analgesics, e.g., acetaminophen.

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, e.g., acetaminophen.

VISCO-3 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, e.g., acetaminophen.

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Policy History/Revision Information

Date	Summary of Changes
4/16/2025	Approved by OptumRx P&T Committee

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

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Archived Policy Versions (Internal Only)

Effective Date	Policy Number	Policy Title
mm/dd/yyyy – mm/dd/yyyy	######	Title of Policy Hyperlinked to KL or Other Internal Location

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
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- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

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Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).

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