# SODIUM HYALURONATE

**Policy Number:** PHARMACY 059.20 T2  
**Effective Date:** September 1, 2012

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The services described in Oxford policies are subject to the terms, conditions and limitations of the Member's contract or certificate. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage enrollees. Oxford reserves the right, in its sole discretion, to modify policies as necessary without prior written notice unless otherwise required by Oxford's administrative procedures or applicable state law. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

Certain policies may not be applicable to Self-Funded Members and certain insured products. Refer to the Member's plan of benefits or Certificate of Coverage to determine whether coverage is provided or if there are any exclusions or benefit limitations applicable to any of these policies. If there is a difference between any policy and the Member's plan of benefits or Certificate of Coverage, the plan of benefits or Certificate of Coverage will govern.

## CONDITIONS OF COVERAGE

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<th>Applicable Lines of Business/Products</th>
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<td>Referral Required</td>
<td>Yes - Office(^1), No - Outpatient</td>
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<td>Referral Required (Non-gatekeeper)</td>
<td>Yes - Office(^2), No - Outpatient</td>
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<td>Authorization Required</td>
<td>Yes - Office(^2), Outpatient(^3)</td>
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<td>Precertification with Medical Director Review Required</td>
<td>No(^4)</td>
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<td>Special Considerations</td>
<td>1Percertification is not required in the office for Oxford's preferred products of Euflexxa, Orthovisc, Synvisc or Synvisc-One (J7323, J7324 and J7325). 2Percertification is required for services covered under the Member's General benefits package when performed in the office of a participating provider. For Commercial plans, precertification is not required, but is encouraged for out-of-</td>
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\(^1\)Percertification is not required in the office for Oxford's preferred products of Euflexxa, Orthovisc, Synvisc or Synvisc-One (J7323, J7324 and J7325).  
\(^2\)Percertification is required for services covered under the Member's General benefits package when performed in the office of a participating provider. For Commercial plans, precertification is not required, but is encouraged for out-of-
Special Considerations (continued)

network services performed in the office that are covered under the Member's General benefits package. If precertification is not obtained, Oxford may review for medical necessity after the service is rendered.

3**Effective 12/01/10, Oxford's Preferred Sodium Hyaluronate Products will be Euflexxa, Orthovisc, Synvisc and Synvisc-One. If coverage has already been provided for a non-preferred Sodium Hyaluronate product, it will continue until the authorization expires. After the authorization expires members will be required to demonstrate that the preferred products are ineffective or cause side effects in order to obtain coverage for a non-preferred product.**

3Precertification with review by a Medical Director or their Designee is required in all sites of service for J7321 and J7326.

**This requirement does not apply to New Jersey lines of business.

COVERAGE RATIONALE

Pre-certification is not required in the office for J7323, J7324, J7325

Initial Course of Administration/Treatment

I. Treatment with intra-articular injections of sodium hyaluronate are considered medically necessary for pain due to osteoarthritis of the knee when administered according to U.S. Food and Drug Administration (FDA) labeled indications.

FDA Labeling*:

<table>
<thead>
<tr>
<th>Product</th>
<th>Number of Injections</th>
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<tr>
<td>Euflexxa</td>
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<tr>
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<tr>
<td>Synvisc-One</td>
<td>1</td>
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<tr>
<td>Gel One</td>
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*Hyaluronic acid preparations for the treatment of pain due to osteoarthritis of the knee are deemed therapeutically equivalent. The Oxford Pharmacy defines therapeutic equivalence as, "when prescription drug products can be expected to produce essentially the same therapeutic outcome and toxicity."

A. **Euflexxa, Orthovisc, Synvisc or Synvisc-One (J7323, J7324, J7325): Pre-certification is not required in the office for J7323, J7324, J7325**

Oxford considers use of intra-articular hyaluronan injections, Euflexxa (1% sodium hyaluronate), Orthovisc (high molecular weight form of hyaluronic acid), Synvisc (Hylan G-F 20) or Synvisc-One (Hylan G-F 20), medically necessary for members with osteoarthritis of the knee who meet all of the following criteria:
1. The member has documented symptomatic osteoarthritis of the knee; **AND**
2. The member reports pain which interferes with functional activities (e.g., ambulation, prolonged standing); **AND**
3. **The member has not responded adequately to conservative therapy which may include physical therapy or pharmacotherapy (e.g. non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen and/or topical capsaicin cream) or injection of intra-articular steroids and such therapy has not resulted in functional improvement after at least 3 months, or the member is unable to tolerate conservative therapy because of adverse side effects; **AND**
4. The pain cannot be attributed to other forms of joint disease; **AND**
5. There are no contraindications to the injections (e.g., active joint infection, bleeding disorder).

**This requirement does not apply to New Jersey lines of business.**

B. Hyalgan and Supartz (J7321) and Gel-One (J7326): Pre-certification is required in all settings for J7321 and J7326

Oxford considers use of intra-articular hyaluronan injections, Hyalgan (sodium hyaluronate) and Supartz (sodium hyaluronate), and Gel-One (hyaluronan) medically necessary for members with osteoarthritis of the knee who have met the criteria above **AND**:

1. **The member has a history of failure, contraindication or intolerance documented trial and failure to Synvisc, Synvisc-One, Euflexxa or Orthovisc.**

**This requirement does not apply to New Jersey lines of business.**

**Note:** There is no evidence that use of one particular intra-articular hyaluronan product is considered to be of greater effectiveness over another.

II. Oxford may consider intra-articular injections of sodium hyaluronate as medically necessary for temporomandibular joint (TMJ) disc displacement and osteoarthritis.

III. Treatment with sodium hyaluronate preparations is not medically necessary, in any joint other than the knee or TMJ or for any other indication not listed above as medically necessary including but not limited to:

- Pain due to osteoarthritis
- Any other form of arthritis [including rheumatoid arthritis (RA)]
- Patello-femoral syndrome
- Chondromalacia of the knee
- Following total or partial knee joint replacement

Increase in viscoelasticity of synovial fluid after sodium hyaluronate injection has not been demonstrated in patients with rheumatoid arthritis, and it has not been determined whether sodium hyaluronate is protective in joints affected by rheumatoid arthritis. Further studies are needed to determine the safety and durability of such treatment for patello-femoral syndrome and chondromalacia of the knee and whether it significantly delays the need for more invasive treatment, e.g. surgery, joint replacement or arthroplasty. There are no clinical studies evaluating the use of sodium hyaluronate in persons following total or partial knee joint replacement surgery.
IV. Treatment with hyaluronic acid gel preparations to improve the skin's contour and/or reduce depressions due to acne, scars, injury or wrinkles is considered cosmetic and is therefore excluded from coverage. The use of sodium hyaluronate preparations to improve the skin's contour and/or reduce depressions in the skin due to acne, scars, injury or wrinkles improves physical appearance but does not remove or improve a functional impairment of the skin.

Subsequent Course of Administration/Treatment

I. Repeated courses of intra-articular sodium hyaluronan injections of the knee may be considered medically necessary under the following conditions:

- Documentation of significant pain relief achieved with the prior course of injections; AND
- Pain has recurred, AND
- At least six (6) months have passed since the prior course of treatment.

BACKGROUND

Sodium hyaluronate, also referred to as hyaluronic acid (HA) or hyaluronan, is a viscoelastic substance that occurs naturally in synovial fluid and is thought to play an important role in lubricating, protecting, and maintaining the health of articular cartilage. Sodium hyaluronate preparations are used as an intra-articular treatment for relief of pain associated with osteoarthritis (OA), with the potential for disease modification through improvement of synovial fluid quality and/or quantity. (Hayes, 2009)

Hyaluronic acid preparations have been approved by the FDA as a device for the treatment of pain in osteoarthritis of the knee in patients who have not responded to exercise, physical therapy and non-prescription analgesics. Hyaluronic acid gels have also been approved by the FDA for treatment of wrinkles and other facial contouring disorders.

CLINICAL EVIDENCE

Numerous randomized controlled trials have investigated the utility of sodium hyaluronate for osteoarthritis of the knee as well as for temporomandibular joint arthritis and disc displacement. There is growing literature regarding the use of Synvisc™ Hylan G-F 20 for the treatment of osteoarthritis (OA) of the hip. However, today, FDA labeling for sodium hyaluronate is limited to osteoarthritis of the knee.

Knee:

A systematic review and meta-analysis by Bannuru et al. (2009) compared the effectiveness of intra-articular hyaluronic acid (n=312 patients) with corticosteroids (n=294 patients) for knee osteoarthritis (OA). Of 1238 studies evaluated, 7 studies were included for meta-analysis. The authors found that intra-articular corticosteroids appeared more effective for pain relief through week 4. At week 4 both treatments appeared equal. However, treatment effects at 8 weeks and beyond showed greater effectiveness in the hyaluronic acid group.

Goldberg and Buckwalter's (2005) meta-analysis of the use of hyaluronans in the treatment of OA concluded that there is clinical evidence to support that in addition to relieving the symptoms of OA, they also modify the structure of the disease joint and the rate of OA disease progression.

A prospective, multi-center, randomized, placebo controlled double-blind study by Jorgensen et al. (2010) compared the use Hyalgan (n=165) with saline (n=170) for knee osteoarthritis. Patients in each group received 5 weekly injections. During the study, 37 patients were dropped from the study for non-compliance with the study protocol leaving 298 patients (139 in Hyalgan group and 159 in the saline group). All patients were followed for 3 months after the first injection. Patients still benefiting from treatment after 3 months were followed until ‘time to recurrence’ or a maximum of 1 year after the first injection. At 3 months, 53 patients in the Hyalgan group and 47
in the saline group did not respond to treatment. Mean time to recurrence was 172 days for the Hyalgan group and 204 days for the saline group. The authors found no differences between the saline and Hyalgan group. Five weekly injections of Hyalgan did not improve pain, function or use of acetaminophen at 3, 6, 9 and 12 months after treatment for knee osteoarthritis.

Chevalier et al. (2010) conducted a prospective double-blind study of 253 patients to compare the use of a single 6ml intra-articular injection of hylan G-F 20 (n=123) with placebo (n=130) in patients with symptomatic knee osteoarthritis. Outcomes were measured by the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, Likert and patient global assessment (PGA) questionnaires as well as a blinded evaluator completed by the clinical observer global assessment (COGA). Patients were followed up 1, 4, 8, 12, 18 and 26 weeks after injection. Patients receiving hylan G-F 20 had greater improvements in WOMAC A pain scores and several of the secondary outcome measures (WOMAC A1, PGA and COGA), than patients receiving placebo treatment. The authors concluded that a single 6 ml intra-articular injection of hylan G-F 20 provided better pain relief over 26 weeks than placebo.

In a prospective, naturalistic study by Petrella (2005), 537 patients received a 3 intra-articular injection series with Suplasyn over 3 weeks. The cohort group was followed for 6.7 years. Patients returned for consideration of a repeat injection series based on their perception of symptom severity and were eligible if their resting visual analog scale pain was > 45 mm. The three-injection series and data collection were repeated, and again, patients were given similar instructions regarding consideration of a third injection series. The mean time between first and second series was 27 +/- 7 wks. Duration of symptom control was about 6 months. These data support the potential role of intra-articular hyaluronic acid as an effective long-term therapeutic option for patients with osteoarthritis of the knee.

Conrozier et al. (2009) conducted a prospective, multi-center, randomized study of 100 patients to evaluate the safety and efficacy of five dosing regimens of viscosupplementation with hylan G-F 20 in patients with symptomatic tibio-femoral osteoarthritis. Patients were randomized to receive varying dosing regimens of hylan G-F 20 (1 x 6 mL, 1 x 4 mL, 2 x 4 mL 2 weeks apart, 3 x 4 mL 1 week apart, or 3 x 2 mL 1 week apart). Patients in the 3 x 4 mL group reported the highest percentage of device-related local adverse events (30%) while patients in the 1 x 6 mL and 3 x 2 mL groups reported only 10%. Patients in the 1 x 6, 3 x 4 and 3 x 2 mL treatment groups showed the greatest improvements in the patient-rated knee osteoarthritis pain assessment visual analog score. The authors concluded that a single 6 mL injection of hylan G-F 20 may be as efficacious, and as well tolerated, as 3 x 2 mL one week apart; however, a double-blind, controlled trial is needed to confirm these data.

Jubb et al. (2003) observed no overall clinical effect of HA; although patients with mild OA had an improvement in joint space narrowing following HA treatment. There was no effect in similar patients treated with the placebo. Petrella et al. (2002) studied the effects of NSAIDs and intra-articular HA and found that both treatments provided similar pain relief at rest for patients with OA of the knee. However, Hylauronate acid appeared to have more effect than NSAIDs when patients were active. Several studies compared intra-articular HA with intra-articular corticosteroid found that both treatments were effective, although long-term relief was generally considered superior with HA. (Frizziero, 2003; Leopold, 2002; Tascioglu, 2003; Caborn, 2004)

National Institute for Health and Clinical Excellence (NICE): A 2008 guidance document states that the mechanism by which hyaluronic acid exerts its therapeutic effect, if any, is not certain, and evidence for restoration of viscoelasticity is lacking. NICE concluded that intra-articular hyaluronan injections are not recommended for the treatment of osteoarthritis.

**Temporomandibular Joint:**

Although sodium hyaluronate has not been labeled by the FDA for use in the temporomandibular joint (TMJ), the evidence from randomized controlled trials indicates that this treatment has a beneficial effect in patients with osteoarthritis or disc disorders of the temporomandibular joint.
In a comparative study by Bjornland et al. (2007), 40 patients with osteoarthritis of the TMJ were randomly divided into two groups to compare the efficacy and complications of intra-articular TMJ injections. The subjects received either two intra-articular injections with sodium hyaluronate or two intra-articular injections with corticosteroids, 14 days apart. The effect of the treatment was evaluated 14 days, 1 and 6 months after the initial injection and was based on the following measurements: pain intensity, pain localization, joint sounds, mandibular function and complications. Both groups of patients had less pain intensity at the 6-month follow-up, and there was significantly less pain intensity in the group of patients receiving sodium hyaluronate compared with corticosteroids. A decrease in crepitation was seen in both groups. In the 20 subjects receiving sodium hyaluronate both the mandibular vertical opening and protrusion increased significantly (P < 0.000). Lateral movement from the affected side increased both in subjects injected with sodium hyaluronate (P = 0.024), and those injected with corticosteroids (P = 0.042). In conclusion, this study confirms that injections in the TMJ with sodium hyaluronate or corticosteroids may reduce pain and improve function in patients with osteoarthritis. The injections were more effective in patients with only TMJ pain compared with patients suffering from both TMJ and myofascial pain. Injection with sodium hyaluronate was significantly more effective in decreasing pain intensity than corticosteroids.

In patients with TMJ pain unresponsive to analgesics, physical therapy, and occlusal adjustment, sodium hyaluronate has been shown to reduce pain and increase range of motion in the joint. This effect can be sustained for several years and appears to be equivalent to corticosteroids without the potential adverse effects associated with chronic steroid use (Gray, 1996; Bertolami, 1993). Sato et al. (2001) found that in a study of 121 patients with disc displacement without reduction who received injections of HA, had significantly improved outcomes as compared to the control group at the one and two year follow-up. Hepguler et al. found that the use of HA in patients with disk displacement with reduction was an effective treatment for reducing pain, joint sounds and signs of clinical dysfunction (Hepguler, 2002). In patients with degenerative TMJ pain unresponsive to analgesics, physical therapy, and occlusal adjustment, sodium hyaluronate has been shown to reduce pain and increase range of motion in the joint. This effect can be sustained for several years and appears to be equivalent to corticosteroids without the potential adverse effects associated with chronic steroid use. (Gray, 1996; Bertolami, 1993)

Long et al. (2009) conducted a randomized controlled trial on 120 patients to compare the outcome of inferior and superior joint space injection of sodium hyaluronate in patients with disc displacement without reduction of the temporomandibular joint (TMJ). Patients were randomized into 2 experimental groups. One group of patients received superior joint space injections of sodium hyaluronate and the other group was treated with inferior joint space injections. Patient's TMJ status and clinical symptoms were evaluated at the 3 and 6 month follow-up appointments. The clinical parameters recorded were maximal mouth opening (MMO), pain intensity on a visual analog scale (VAS), and modified Helkimo's clinical dysfunction index and analyzed with ANCOVA. Fifty of the superior and 54 of the inferior joint space injection therapy group returned for the 3 and 6 month evaluations. Both groups had improvement in the clinical parameters at the 3 and 6 month follow-ups; however, the inferior joint injection group at 3 months had a greater reduction in TMJ pain compared with the superior joint injection group. The authors concluded that inferior joint space injection with sodium hyaluronate is a valid method of treating disc displacement without reduction of TMJ and a long-term study will be needed to assess the effect of inferior joint injection on the morphologic changes of the TMJ.

Firestein: Kelley's Textbook of Rheumatology, 8th ed., 2008 edition states that intra-articular injection of high-molecular-weight sodium hyaluronate may be given twice, 2 weeks apart (Firestein, 2008). Use of sodium hyaluronate has been shown to have essentially the same therapeutic effect as steroid injections without the potential adverse side effects.

Shoulder:
A randomized, double-blind, placebo-controlled study by Chou et al. (2010) evaluated the use of sodium hyaluronate in 51 patients with rotator cuff lesions without complete tears. Patients received either weekly injections of sodium hyaluronate or normal saline for 5 weeks. Outcomes were measured using a Constant score, which measures shoulder function, and visual analog
The Constant score and visual analog scale improved every week throughout treatment for both groups. However the treatment group showed greater improvement. The authors concluded that subacromial injections of sodium hyaluronate may be an alternative treatment in patients with rotator cuff lesions. The study is limited by small sample size and lack of comparison to other treatments such as subacromial steroid injection.

Blaine et al. (2008) conducted a double-blind randomized controlled trial of 660 patients to evaluate the use of sodium hyaluronate (Hyalgan) to treat persistent shoulder pain. Patients were equally randomized to receive either 5 weekly intra-articular injections of sodium hyaluronate, 3 weekly intra-articular injections of sodium hyaluronate followed by 2 weekly intra-articular injections of saline solution, or 5 weekly intra-articular injections of saline solution over 26 weeks. Patients were evaluated at baseline and at 7, 9, 13, 17, and 26 weeks after the initiation of treatment. Outcomes were measured by a reduction in shoulder pain during movement in the previous 24 hours with use of a visual analog scale at the 13 week follow-up visit as well as maintenance of visual analog scale pain relief through the 26 week period. At 7 weeks, the 5 injection hyaluronate group began to show improvement; at week 17, the 3 injection hyaluronate group began to show improvement and the 5 injection hyaluronate group maintained improvement; and at 26 weeks, the 3 injection hyaluronate maintained improvement. Patients with osteoarthritis demonstrated significantly better visual analog scale shoulder pain scores after hyaluronate treatment than those without osteoarthritis. At 26 weeks, 456 patients completed the study. The most common reasons for study discontinuation were lack of efficacy (82 patients), patient withdrawal of consent (54 patients), and loss to follow-up (11 patients). There were no meaningful differences between the groups for these reasons. Although the original endpoint of pain reduction at 13 weeks was not achieved the maintenance of pain relief at 26 weeks, as a secondary endpoint, was achieved. The patients with osteoarthritis who received Hylan (5 or 3 injections) achieved and maintained reductions in pain and improved function by week 26. There was no difference in pain reduction for patients without osteoarthritis between the three treatment groups; however, a significant treatment effect was observed in the control group. The three-injection option may decrease time, expenditure and discomfort associated with the injection process. The authors concluded that the use of sodium hyaluronate is effective and well tolerated for the treatment of osteoarthritis and persistent shoulder pain in patients with shoulder pain who do not achieve adequate relief with analgesics, nonsteroidal anti-inflammatory drugs, or corticosteroids and who are not candidates for surgical intervention. However, additional work is needed to determine those who might benefit more from one regimen over the other and whether these regimens may be associated with variable outcomes not fully evaluated in this study (e.g., longer-term duration of benefit).

A prospective, multi-center study by Noel et al. (2009) evaluated the use of sodium hyaluronate (Hylan G-F 20 or Synvisc-One) in 33 patients with shoulder osteoarthritis and an intact rotator cuff. Baseline measurements included a visual analog score between 59 and 64 / 100 and documentation of shoulder osteoarthritis with an osteophyte at the lower part of the humeral head measuring at least 2mm along the long axis. Follow-up was 6 months. All patients received an intra-articular injection of 2ml of Hylan G-F 20 given under fluoroscopic guidance. Patients with visual analog scores between 40 and 90 received a second injection after 1 (n=7), 2 (n=4), or 3 (n=5) months. The mean VAS pain score decreased from an average of 61.2mm at baseline to 37.1mm after 3 months. Outcomes were measured utilizing visual analog scales. Twenty-nine patients completed the study; 4 dropped out due to unacceptable pain but it was not specified if these patients received one or two injections. The authors concluded that one or two intra-articular injections of Hylan GF 20 may be a valid option in patients with shoulder osteoarthritis with an osteophyte of at least 2mm on the long axis and an intact cuff. However further studies are needed to validate the results and determine the optimal treatment frequency and appropriate patient selection criteria. The study is limited by small sample size, lack of comparison to a control group and manufacturer sponsorship.

A prospective study by Brander et al. (2010) evaluated the use of 2 intra-articular injections of Hylan G-F 20 in 36 patients with shoulder arthritis who had failed 3 months of standard treatment. After injection, patients had equal or greater than 20% improvement in visual analog scale scores. Seven patients reported either increased pain (n=3) at 6 months or no pain relief (n=4).
Despite these results, the authors concluded that 2 injections of Hylan G-F 20 should be considered for treating shoulder arthritis. The study is limited by small sample and lack of comparison to a control group.

**Hip:**
A multicenter, randomized, placebo-controlled trial by Richette et al. (2009) of 85 patients with symptomatic hip OA (pain score of >40 mm on a visual analog scale [VAS]) and a Kellgren/Lawrence grade of 2 or 3. Patients were randomized to the hyaluronic acid (HA) group (n = 42) or placebo group (n = 43) and followed for 3 months. At 3 months, the decrease in pain score did not differ between the HA and placebo groups in the intent-to-treat analysis (mean +/- SD decrease 7.8 +/- 24.9 mm with HA versus 9.1 +/- 27.4 mm with placebo; P = 0.98). The authors concluded that the findings indicate that a single IA injection of HA is no more effective than placebo in treating the symptoms of hip OA.

A multi-center clinical trial by Conrozier, et al. (2006), 56 patients were evaluated following one intra-articular injection of hylan G-F 20. The results suggest that hylan G-F 20 is an effective treatment of symptomatic OA of the hip, particularly in less severe radiological cases. In a clinical trial by Migliore et al., 30 patients with symptomatic hip OA were treated with hylan G-F 20 under ultrasound guidance. Lequesne index, VAS scale of hip pain, and NSAID consumption were evaluated at baseline as well as 2 and 6 months after the beginning of the treatment. The study results showed a reduction in the Lequesne index, VAS scale of hip pain, and NSAID consumption that was statistically significant to the baseline. In a systematic review by Fernandez and Ruano-Ravina, a total of 8 studies, comprising clinical trials and one review were evaluated (Fernandez, 2006). It was concluded that HA treatment should only be used under careful supervision by the clinician and just in those cases where other treatments have failed in hip OA.

A prospective double-blind trial by Migliore et al. (2009) of 42 patients with osteoarthritis of the hip compared the use of intra-articular bacterial-derived hyaluronic acid (Hyalubrix®) (HA) with local analgesia (mepivacaine). Outcomes were measured by the Lequesne algofunctional index (grades 1 to 4), visual analog scale (VAS), and the patient's global assessment score for hip OA. Patients receive 2 monthly injections. Both groups showed improvement from baseline. However, the hyaluronic acid group showed greater improvement in Lequesne algofunctional index and VAS scores. The authors concluded that intra-articular hyaluronic acid may be a treatment option for patients with osteoarthritis of the hip. The study is limited by small sample size and lack of a control group.

Use of HA has been approved in Europe for hip pain and is in clinical trials in the US. Clinical trials are also in the process for use of HA in shoulder and ankle joints in Europe.

**Ankle Osteoarthritis:**
A study by Mei-Dan et al. (2010) evaluated the efficacy of sodium hyaluronate to treat ankle osteoarthritis in 16 patients. Patients underwent 5 weekly injections and were followed for 32 weeks. Improvement in pain was seen in 13 of the 15 patients for the duration of the study. One patient was dropped from follow-up due to unrelated surgery. Range of motion improved by 20% and there was a reduction in pain assessed by visual analog scale and ankle-hindfoot scores. The authors concluded that intra-articular injection of sodium hyaluronate for ankle osteoarthritis is a viable treatment option. The study is limited by small sample size, lack of a control group and lack of baseline data for range of motion and pain.

**Rheumatoid Arthritis:**
There is controversy regarding the underlying biological basis for use of sodium hyaluronate for the treatment of RA. There is some evidence that sodium hyaluronate inhibits synovial cell proliferation and suppresses lymphocyte proliferation, both of which occur in RA patients (Matsuno, 1999). Furthermore, sodium hyaluronate has been shown to inhibit the release of proteoglycans from articular cartilage, a finding that suggests that there may be a reduction in degeneration of the cartilage (Matsuno, 1999). In patients with osteoarthritis, sodium hyaluronate increases the viscoelasticity of synovial fluid, which plays a key role in cushioning and protecting
the joint. However, an increase in viscoelasticity of synovial fluid after sodium hyaluronate injection has not been demonstrated in patients with RA, and it has not been determined whether sodium hyaluronate is protective in joints affected by RA. Wang (2002) concluded that glycosaminoglycans (Hyaluronic Acid) may be a potential cause of rheumatoid arthritis. Majeed (2004) found that the high hyaluronic acid levels correlated with early rheumatoid arthritis disease activity.

**Patello-Femoral Syndrome or Chondromalacia:**
Review of the literature resulted in one study by Jiang et al. (2007) regarding the use of sodium hyaluronate for treatment of chondromalacia. This study was uncontrolled, and is insufficient to conclude that sodium hyaluronate is effective for treatment of chondromalacia. In the study, Jiang et al. explored the use of sodium hyaluronate (visco-elastic material) for joint cavity filling combined with exercise for power in the treatment of chondromalacia patellae. The experiment was carried out among 179 knees of 120 patients with knee osteoarthritis from April 2003 to May 2006. At the 90 degrees angle of knee flexion, the patella was injected with 2 mL sodium hyaluronate solution, once per week, and 5 times were taken as a course. Meanwhile, isometric exercise for strengthening medial vastus muscle was accompanied. The result showed that after 5-week exercise, the rate of excellent and good curative effects was 91.1%, and overall response rate reached 98.9%. Excellent: disappearance of knee joint pain and rigidity, free movement, knee joint flexion > 130degrees and extension at 0 degrees in 102 knees; Good: basic disappearance of knee joint pain and rigidity, limited movement, knee joint flexion > 110degrees and extension at 0 degrees in 61 knees; Fair: occasional disappearance of knee joint pain and rigidity, recovery after rest, limited movement, knee joint flexion 90 degrees and extension at 0 degrees in 14 knees; Ineffective: no improvements of knee joint pain and rigidity after injection, severely limited movement, knee joint flexion < 90degrees and extension at 0 degrees in 2 knees.

**Joint Replacement:**
There are no clinical studies evaluating the use of sodium hyaluronate in persons following total or partial joint replacement surgery.

**Treatment of Skin Contours and Depressions:**
While sodium hyaluronate can fill in contours, the presence of depressions and/or wrinkles is not a functional impairment. Use of sodium hyaluronic gel for these indications is cosmetic.

**Professional Societies:**

*The American College of Rheumatology (ACR)* published *Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee* and concluded that intra-articular hyaluronan injections may be especially advantageous in patients whom- nonselective NSAIDs and COX-2-specific inhibitors are contraindicated, or in whom they have been associated either with a lack of efficacy or with adverse events (ACR, 2000).

*The American Academy of Orthopaedic Surgeons (AAOS)* A 2008 guideline on the Treatment of Osteoarthritis of The Knee (non-arthroplasty), states that that AAOS cannot recommend for or against the use of intra-articular hyaluronic acid for patients with mild to moderate symptomatic OA of the knee.

*The Agence d’ des technologies et des modes d’intervention en sant (AETMIS)* as well, reached similar conclusions to the draft NICE guidance (Dagenais, 2007). The AETMIS assessment concluded that viscosupplementation offers clinically modest relief from the symptoms of knee osteoarthritis over a period that could last up to several weeks offering safe short-term treatment. The assessment noted, however, that these conclusions are based on secondary analyses of a multitude of small primary studies of poor methodological quality. AETMIS reported that available data did not help distinguish differences in the effectiveness of any one product over the others. It was equally impossible to identify patient subgroups more likely to benefit from this treatment compared with other currently available therapeutic modalities. AETMIS concluded that, given the modest effectiveness of viscosupplementation compared with its relatively high cost and the additional professional resources required to administer it, it is not
currently justified to contemplate funding viscosupplementation for all patients with osteoarthritis of the knee. The assessment noted, however, that it is possible that viscosupplementation could be offered as a last-resort treatment to patients who do not achieve pain relief from conventional therapies or for whom these are contraindicated.

A 2009 *Agency for Healthcare Research and Quality (AHRQ)* Clinician’s Guide summarized the evidence on the effectiveness and safety of viscosupplementation for osteoarthritis of the knee. AHRQ found that:

- Any clinical improvement attributable to viscosupplementation is likely small and not clinically meaningful
- Some trials suggest better clinical response to the highest molecular weight hyaluronan product, while other trials have not confirmed this finding. Overall, evidence is insufficient to demonstrate clinical benefit for the higher molecular weight products.
- Evidence is insufficient to determine whether the frequency of adverse events is higher with repeat injections.

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

**Osteoarthritis**

Sodium hyaluronate has been approved and is marketed as a device for intra-articular treatment of pain due to osteoarthritis of the knee because it acts mechanically, as a lubricant, rather than by absorption into the body as would a drug.

The FDA has approved the following labeling instructions as single-treatment regimens consisting of 1 to 5 injections in patients who have failed conservative therapy with exercise and simple analgesics:

- Hyalgan - approved for 5 injections
- Synvisc and Euflexxa - approved for 3 injections
- Supartz - approved for 3-5 injections
- Orthovisc - approved for 3-4 injections
- Synvisc One - approved as a single injection
- Gel-One – approved as a single injection

**Contraindications:**

- *Do not administer to patients with known allergies to avian or avian-derived products (including eggs, feathers, or poultry). Contraindication for Orthovisc only. None of the other avian derived preparations listed this as a contraindication.
- Do not administer to patients with known hypersensitivity (allergy) to hyaluronate preparations.
- Do not inject sodium hyaluronate into the knees of patients with infections or skin diseases in the area of the injection site or joint.

None of the hyaluronic acid preparations are approved for use in joints other than the knee. Additional information (product code MOZ) is available at: [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/listing.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/listing.cfm). Accessed March 5, 2012

Synvisc-One (hylan G-F 20) received premarket approval February 26, 2009 and 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). Additional information on Synvisc-One is available at: [http://www.accessdata.fda.gov/cdrh_docs/pdf/P090015S012b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf/P090015S012b.pdf). Accessed March 5, 2012

Gel-One (hyaluronan) received FDA premarket approval on March 22, 2011.
These products have not specifically been labeled for the treatment of rheumatoid arthritis or cosmetic applications or to treat osteoarthritis other than in the knee.

**Skin Contouring (including acne, scars and wrinkle treatments)**
The FDA has approved several products containing a transparent hyaluronic acid gel to improve the contours of the skin. These products are used to treat acne, scars and wrinkles on the skin by temporarily adding volume to facial tissue and restoring a smoother appearance to the face. Devices include:


- Perlane® injectable gel received PMA approval May 2, 2007. Additional information is available at: [http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm077009.htm](http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm077009.htm). Accessed March 5, 2012.


- Juvéderm 24HV, Juvéderm 30 & Juvéderm 30HV Gel Implants received PMA approval June 2, 2006. Additional information is available at: [http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm078154.htm](http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm078154.htm). Accessed March 5, 2012.

**Additional Products**
Hyalubrix (not known to be marketed in the U.S.)

**APPLICABLE CODES**

*The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the Member’s plan of benefits or Certificate of Coverage. This list of codes may not be all inclusive.*

**Applicable CPT Codes**

<table>
<thead>
<tr>
<th>CPT® Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>20605</td>
<td>Arthrocentesis, aspiration and/or injection; intermediate joint or bursa (eg, temporomandibular, acromioclavicular, wrist, elbow or ankle, olecranon bursa)</td>
</tr>
<tr>
<td>20610</td>
<td>Arthrocentesis, aspiration and/or injection; major joint or bursa (eg, shoulder, hip, knee joint, subacromial bursa)</td>
</tr>
</tbody>
</table>

*CPT® is a registered trademark of the American Medical Association.*

**Applicable HCPCS Codes**

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7321</td>
<td>Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular</td>
</tr>
</tbody>
</table>
Reimbursable ICD-9 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-9 Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>524.62</td>
<td>Arthralgia of temporomandibular joint</td>
</tr>
<tr>
<td>524.63</td>
<td>Articular disc disorder (reducing or non-reducing) of temporomandibular joint</td>
</tr>
<tr>
<td>524.69</td>
<td>Other specified temporomandibular joint disorders</td>
</tr>
<tr>
<td>715.16</td>
<td>Primary localized osteoarthritis, lower leg</td>
</tr>
<tr>
<td>715.26</td>
<td>Secondary localized osteoarthritis, lower leg</td>
</tr>
<tr>
<td>715.36</td>
<td>Localized osteoarthritis not specified whether primary or secondary, lower leg</td>
</tr>
<tr>
<td>715.96</td>
<td>Osteoarthritis, unspecified whether generalized or localized, lower leg</td>
</tr>
<tr>
<td>716.56</td>
<td>Unspecified polyarthropathy or polyarthritis, lower leg</td>
</tr>
<tr>
<td>716.86</td>
<td>Other specified arthropathy, lower leg</td>
</tr>
<tr>
<td>716.96</td>
<td>Unspecified arthropathy, lower leg</td>
</tr>
<tr>
<td>719.46</td>
<td>Pain in joint, lower leg</td>
</tr>
</tbody>
</table>

Reimbursable ICD-9 Procedure Codes

<table>
<thead>
<tr>
<th>ICD-9 Procedure Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>76.96</td>
<td>Injection of therapeutic substance into temporomandibular joint</td>
</tr>
<tr>
<td>81.92</td>
<td>Injection of therapeutic substance into joint or ligament</td>
</tr>
</tbody>
</table>

Coding Clarification:
Sodium Hyaluronate is not reimbursable for any other diagnosis not listed as reimbursable and for any other form of arthritis other than osteoarthritis of the knee and TMJ or for any other condition not included in this policy.

ICD-10 Codes (Preview Draft)
In preparation for the transition from ICD-9 to ICD-10 medical coding on October 1, 2014, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. *The effective date for ICD-10 code set implementation is subject to change.*

<table>
<thead>
<tr>
<th>ICD-10 Diagnosis Code (Effective 10/01/14)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M07.661</td>
<td>Enteropathic arthropathies, right knee</td>
</tr>
<tr>
<td>M07.662</td>
<td>Enteropathic arthropathies, left knee</td>
</tr>
<tr>
<td>M07.669</td>
<td>Enteropathic arthropathies, unspecified knee</td>
</tr>
<tr>
<td>M12.861</td>
<td>Other specific arthropathies, not elsewhere classified, right knee</td>
</tr>
<tr>
<td>M12.862</td>
<td>Other specific arthropathies, not elsewhere classified, left knee</td>
</tr>
<tr>
<td>M12.869</td>
<td>Other specific arthropathies, not elsewhere classified, unspecified knee</td>
</tr>
<tr>
<td>M12.9</td>
<td>Arthropathy, unspecified</td>
</tr>
<tr>
<td>M13.0</td>
<td>Polyarthritis, unspecified</td>
</tr>
<tr>
<td>M17.0</td>
<td>Bilateral primary osteoarthritis of knee</td>
</tr>
<tr>
<td>M17.10</td>
<td>Unilateral primary osteoarthritis, unspecified knee</td>
</tr>
</tbody>
</table>
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
M25.561 Pain in right knee
M25.562 Pain in left knee
M25.569 Pain in unspecified knee
M26.62 Arthralgia of temporomandibular joint
M26.63 Articular disc disorder of temporomandibular joint
M26.69 Other specified disorders of temporomandibular joint

REFERENCES

The foregoing Oxford policy has been adapted, in part, from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2012T0078M]


**POLICY HISTORY/REVISION INFORMATION**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/14/2012</td>
<td>Added list of applicable ICD-10 codes (preview draft) in preparation for the transition from ICD-9 to ICD-10 medical coding on 10/01/14</td>
</tr>
</tbody>
</table>

| 09/01/2012 | Updated conditions of coverage/authorization requirements; added language to clarify:  
|           | Pre-certification is required in both the office and outpatient settings (special considerations apply as noted)  
|           | Pre-certification with review by a Medical Director or their Designee is required in all sites of service for HCPCS codes J7321 and J7326  
|           | Revised coverage rationale for initial course of administration/treatment; removed language indicating New Jersey plan Members do require pre-certification for HCPCS codes J7321 and J7326  
|           | Revised list of applicable HCPCS codes; removed language indicating New Jersey plan Members do require pre-certification for HCPCS codes J7321 and J7326  
|           | Added list of applicable (reimbursable) ICD-9 procedure codes: 76.96 (injection of therapeutic substance into temporomandibular joint) and 81.92 (injection of therapeutic substance into joint or ligament)  
|           | Archived previous policy version PHARMACY 059.19 T2 |