Viscosupplementation

Number: 0179

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Aetna considers viscosupplementation medically necessary for members with osteoarthritis of the tibiofemoral articulation of the knee who meet all of the following selection criteria:

A. Conservative therapy (including physical therapy, pharmacotherapy (e.g., non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen (up to 1 g 4 times/day) and/or topical capsaicin cream)) has been attempted in each joint to be treated with viscosupplements and 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

B. The clinical diagnosis is supported by radiologic evidence of osteoarthritis of the knee such as joint space narrowing, subchondral sclerosis, osteophytes and subchondral cysts, or, if radiographs are not available, the member has documented symptomatic osteoarthritis of the knee according to American College of Rheumatology (ACR) clinical and laboratory criteria, which requires knee
pain and at least 5 of the following:

1. Bony enlargement
2. Bony tenderness
3. Crepitus (noisy, grating sound) on active motion
4. Erythrocyte sedimentation rate (ESR) less than 40 mm/hr
5. Less than 30 minutes of morning stiffness
6. No palpable warmth of synovium
7. Over 50 years of age
8. Rheumatoid factor less than 1:40 titer (agglutination method)
9. Synovial fluid signs (clear fluid of normal viscosity and WBC less than 2000/mm3); and

C. The member has failed to adequately respond to aspiration and injection of intra-articular steroids; and
D. The member reports pain which interferes with functional activities (e.g., ambulation, prolonged standing); and
E. The pain cannot be attributed to other forms of joint disease; and
F. The member is not scheduled to undergo a total knee replacement within six (6) months of starting treatment; and
G. There are no contraindications to the injections (e.g., active joint infection, bleeding disorder, skin infections at the injection site).

Note: Ultrasound guidance, fluoroscopic guidance and knee arthrography for viscosupplement injections is considered experimental and investigational because it has not been established that this approach will improve health outcomes.

Additional series of injections for members who have responded to previous series are considered medically necessary under the following circumstances:
A. At least 3 months has elapsed since the prior series of injections; and
B. The medical record demonstrates a reduction in the dose of NSAIDs (or other analgesics or anti-inflammatory medication) during the 3-month period following the previous series of injections (Note: a dose reduction is not required if the member requires these medications for a comorbid medical condition in addition to knee osteoarthritis); and
C. The medical record objectively documents significant improvement in pain and functional capacity as the result of the previous injections.

II. Aetna considers viscosupplementation experimental and investigational for all other indications such as chondromalacia patellae, facet joint arthropathy, following anterior cruciate ligament reconstruction, meniscectomy, or total knee arthroplasty; hemophilic arthropathy, osteochondritis dissecans, palendromic rheumatism, patellofemoral arthritis, patellofemoral syndrome (patellar knee pain), peripheral nerve pain, plantar nerve entrapment syndrome, psoriatic arthritis, or for use in joints other than the knee (e.g., ankle, carpo-metacarpal joint, elbow, hip, metatarso-phalangeal joint, shoulder, thumb, and temporomandibular joint) because the effectiveness of viscosupplementation for these indications has not been established.

III. Aetna considers intra-articular polynucleotides in the treatment of knee osteoarthritis experimental and investigational because the effectiveness of this approach has not been established.

IV. Aetna considers viscosupplementation in combination with anesthetics, corticosteroids, or platelet rich plasma experimental and investigational because the effectiveness of these combinations has not been established.

Least Cost Medically Necessary Brands of Viscosupplement:
There are several brands of viscosupplement on the market. There is a lack of reliable evidence that any one brand of viscosupplement is superior to other brands for medically necessary indications. Euflexxa (1% sodium hyaluronate), Monovisc (high molecular weight hyaluronan) and Orthovisc (high molecular weight form of hyaluronic acid) brands of viscosupplement ("least cost brands of viscosupplement") are less costly to Aetna. Consequently, because other brands of viscosupplement (e.g., Durolane (hyaluronic acid), Gelsyn-3 (sodium hyaluronate), GenVisc 850 (sodium hyaluronate), Hyalgan (sodium hyaluronate), Hymovis (high molecular weight hyaluronan), Supartz (sodium hyaluronate), Synvisc (Hylan G-F 20), Gel-One (cross-linked hyaluronate), and Synvisc One (Hylan G-F 20)) are more costly than these least cost brands of viscosupplement, and least cost brands of viscosupplement are at least as likely to produce equivalent therapeutic results, no other brands of viscosupplement will be considered medically necessary unless the member has a documented contraindication or intolerance to the 3 least cost brands of viscosupplement, Euflexxa, Monovisc, and Orthovisc.

**Background**

Osteoarthritis (OA) is the most common joint disorder and is a leading cause of disability, significantly affecting a patient’s quality of life. Knee OA, in particular, is the most common cause of mobility dependency. The heavy economic impact of OA is a product of the cost of chronic medication use as well as decreased productivity, as it is a leading cause of lost productive work time.

Osteoarthritis (OA) of the knee is a disease in which the elastoviscous properties of the synovial fluid in the knee joint becomes diminished, resulting in less protection and shock absorption. Articular cartilage, made up of collagen and proteoglycans, allows for joint motion without friction and also acts as a shock absorber during impact. In OA, degeneration of the articular cartilage causes significant pain and loss of movement as bone rubs against bone.
OA can be classified as either primary or secondary. Primary OA involves the breakdown of cartilage by proteolytic enzymes called metalloproteinases (MMP) that are released by chondrocytes. What causes these MMP to be released, however, is still unknown. Secondary OA is due to mechanical damage caused by a variety of factors, including but not limited to trauma, muscle atrophy, and abnormal joint loading (associated with obesity).

Since the etiology of primary OA is not well understood and because there are no therapies to prevent or alter the disease process, the goals of therapy for patients with OA are relief of pain and improvement of joint function.

The American Academy of Orthopaedic Surgeons has developed evidence based guidelines for the step-wise approach to treatment of patients with OA. According to these guidelines, physical therapy and exercise programs are baseline therapies and should be prescribed for all patients diagnosed with OA either before or in conjunction with pharmacologic therapies. Physical therapy includes general conditioning, muscle strengthening, and range of motion exercises. In addition, durable medical equipment such as devices for ambulation assistance, appropriate footwear, and bracing should be considered if appropriate.

Symptomatic relief should first be addressed with simple analgesics, including acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs), either selective or nonselective, depending on patient specific factors. Patients should be reassessed in 1-4 weeks. For patients that have failed therapy, imaging tests should be performed and further patient education and physical therapy options should be sought out.

Tramadol and opioids may be used as adjuncts for pain relief if necessary. If systemic therapy is ineffective, topical therapy with capsaicin, topical NSAIDs, or topical salicylates may be considered for short-term management of mild-moderate pain. Some controlled studies show the benefit of
glucosamine/chondroitin combinations in subgroups of OA patients as well.

In cases where simple analgesics have been deemed ineffective, intra-articular injections may provide benefit. Intra-articular glucocorticoid injections are approved for short-term therapy only, as long term therapy has been shown to cause further damage to the joint. Controlled studies show that intra-articular injections of hyaluronate improve joint symptoms and may be effective in patients with mild-moderate degenerative joint disease of the knee.

Hyaluronan, also known as sodium hyaluronate, is a natural complex sugar of the glycosaminoglycan family that is produced by the body and found in high amounts in the joints. The body’s own hyaluronan acts as a lubricant and shock absorber and is needed in order for the joint to work properly.

Viscosupplements such as Euflexxa, Gel-One, GenVisc 850, Hyalgan, Hymovis, Monovisc, Orthovisc, Supartz, Synvisc, and Synvisc-One are indicated for the treatment of pain in patients with osteoarthritis of the knee who have failed to respond to conservative nonpharmacologic therapy with simple analgesics. Safety and effectiveness of use in joints other than the knee has not been established.

In May 1997, the Food and Drug Administration (FDA) approved sodium hyaluronate (Hyalgan), an injectable form of hyaluronic acid (HA), for the treatment of pain associated with knee OA. In November 1996, the Orthopedics and Rehabilitation Devices Panel of the FDA recommended Synvisc for approval in the United States, with the condition that a post-market study be performed. Hylan G-F 20 (Synvisc and Synvisc One), a cross-linked preparation of hyaluronan, is a viscosupplementation drug injected into knee joints to increase the elastoviscous properties of arthritic joint (synovial) fluid, while at the same time slowing its egress from the joint. Trials have indicated that both compounds appear to result in a small but statistically significant improvement in reducing pain and increasing levels
of mobility in the majority of individuals treated, as compared with placebo, and may even slow down deterioration of joints.

Sodium hyaluronate is available as Hyalgan as a 10 mg/mL solution in 2 mL vials and 2 mL pre-filled syringes for intra-articular injection. Hyalgan (sodium hyaluronate) is usually given as weekly intra-articular injections administered for up to 5 weeks, for a total of 5 injections. Some patients may benefit with a total of 3 injections given at weekly intervals. Noticeable improvements usually occur beginning at week 5 after treatment initiation, and symptom relief may last for 6 months. Hyalgan should not be used to treat joint dysfunction. In clinical trials, patients experienced pain relief through Week 26. There is no published data on the safety or efficacy of retreatment.

Supartz (sodium hyaluronate) was approved by the FDA on January 24, 2001. It is indicated for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy (e.g., physical therapy) and simple analgesics (e.g., acetaminophen).

Sodium hyaluronate is available as Supartz as a 10mg/mL solution in 2.5 mL pre-filled syringes for intra-articular injection. Supartz is administered by an injection once-weekly for a total of 5 injections. There is no published data on the safety or efficacy of retreatment.

Sodium hyaluronate is available as Euflexxa as a 10 mg/mL solution in 2 mL pre-filled syringes for intra-articular injection. Euflexxa (sodium hyaluronate) is three intra-articular injections, of 2 mL each, given one week apart. The labeling states that there is no published data on the safety or efficacy of retreatment.

Two formulations of Hylan GF-20 are currently available: Synvisc as a 16 mg/2 mL solution in 2 mL pre-filled syringes and Synvisc-One as a 48 mg/6 mL solution in 6 mL pre-filled syringes for intra-articular injection. Synvisc is administered once-weekly for a total of 3 intra-articular injections, and Synvisc One is
administered in a single intra-articular injection. Published data regarding retreatment with Synvisc demonstrated safety only.

High molecular weight hyaluronan is available as Orthovisc as a 30 mg/2 mL solution in 2 mL pre-filled syringes for intra-articular injection. Orthovisc (hyaluornan) is injected once weekly for 3 to 4 weeks, for a total of 3 to 4 injections. Clinical trials showed patients experienced pain relief for 22 weeks. There is no published data on the efficacy of retreatment.

Sodium hyaluronate is available as GenVisc 850 as 10 mg/mL solution in 3-mL pre-filled syringes for intra-articular injection. GenVisc 850 (sodium hyaluronate) is administered by intra-articular injection. A treatment cycle consists of five injections given at weekly intervals. Some patients may experience benefit with three injections given at weekly intervals. The effectiveness of less than three injections has not been evaluated. The effectiveness of repeat treatment cycles of GenVisc 850 has not been established.

Cross-linked hyaluronate is available as Gel-One in a 30 mg/3mL solution in 3-mL prefilled glass syringes. Gel-One (cross-linked hyaluronate) is one 3.0 mL injection. Safety and effectiveness of a repeat treatment cycle have not been established.

Sodium hyaluronate 0.84% is supplied as Gelsyn-3 (formerly Gel-Syn) is supplied 8.4 mg/mL in a 2 mL pre-filled glass syringe. Gelsyn-3 (sodium hyaluronate 0.84%) is injected once weekly for 3 consecutive weeks, for a total of 3 injections.

Hyaluronic Acid is available as Monovisc in 22 mg/mL solution in a 5.0 mL syringe containing 4.0 mL of Monovisc for intra-articular injection. Monovisc (hyaluronic acid) is one 5.0 mL injection.

Hyaluronic acid is available as Hymovis as a set of 2 single-use 5mL syringes, each containing a 3mL dose of treatment for intra-articular injection. Hymovis (hyaluronic acid) has a treatment cycle of two injections containing 3 mL dose of
treatment one week apart. The effectiveness of repeat treatment cycles of Hymovis has not been established.

There is a lack of reliable evidence that any one brand of viscosupplement is superior to other brands for medically necessary indications. There are also a lack of studies demonstrating that persons who fail to respond to one brand of viscosupplement will respond to other brands of viscosupplements.

There is a lack of evidence in the peer-reviewed published medical literature on the impact of fluoroscopic guidance in improving clinical outcomes of viscosupplementation injections of the knee. There are no published peer-reviewed clinical studies demonstrating improved outcomes of viscosupplementation of the knee when administered with fluoroscopic guidance.

In 2000, the American College of Rheumatology (ACR) updated its guidelines for the treatment of OA of the knee. In mild symptomatic OA, treatment may be limited to patient education, physical and occupational therapy and other non-pharmacologic modalities, and pharmacologic therapy including non-opioid oral and topical analgesics. In patients who are unresponsive to this regimen, the use of NSAIDs is appropriate.

According to ACR guidelines, intra-articular injections of corticosteroids or hyaluronic may be used for patients who fail to respond to management that is more conservative. Patients with severe symptomatic OA of the knee may require surgical intervention, e.g., osteotomy or total joint arthroplasty. The guidelines on knee pain from the American College of Orthopedic Surgeons (1999) and the National Institute for Health and Clinical Excellence (2007) also recommend use of intra-articular steroids in patients with OA of the knee that fail to respond to more conservative measures (e.g., NSAIDs or acetaminophen, physical therapy, decreased activity). According to the literature, patients with joint effusions and local tenderness may have greater benefit from intra-articular
steroid injections. Neither patient function, radiographic features, intra-articular crystals nor a raised synovial fluid cell count predict a good response (Creamer, 1997). At the basic science level, there are a number of mechanisms by which the improvement is thought to occur -- mRNA synthesis, B and T cell function, cytokine levels, metalloproteases and synovial permeability (Creamer 1997, Genovese 1998). The benefits of corticosteroids may also be due to relief of effusions from aspiration and disruption of adhesions within the joint. Although there are only a limited number of studies that have directly compared the viscosupplementation with corticosteroid injections, these studies indicate that corticosteroid injections are as effective as viscosupplementation in the treatment of OA of the knee (Johnston, 2003). The most serious complication is septic arthritis, with an incidence of 1/17,000 to 1/50,000 (SCHIN, 2002). There is a risk of local tissue atrophy and depigmentation, particularly when small joints are injected with potent corticosteroids. Concern about progressive joint damage following repeated corticosteroid injections is controversial; despite the large number of people treated with intra-articular corticosteroids, case reports that suggest this may result in joint damage are rare (SCHIN, 2002). According to available literature, it is inadvisable to treat patients with a complete collapse of joint space or bone loss with intra-articular hyaluronic acid or corticosteroids, given their poor clinical response (Evanich et al, 2001).

Viscosupplementation is a therapeutic modality for the treatment of osteoarthritis based on the physiologic importance of hyaluronan in synovial joints (Bellamy, 2002). Its therapeutic goal is to restore the visco-elasticity of synovial hyaluronan, thereby decreasing pain, improving mobility and restoring the natural protective functions of hyaluronan in the joint. The short-term mode of action of viscosupplementation is believed to be based on the pain relieving effect of the elastoviscous fluid in the affected joint. In the long-term, the restoration of the joint mobility due to relief of pain triggers a sequence of events, which restores the trans-synovial flow and
subsequently the metabolic and rheological homeostasis of the joint.

According to a review of the literature in the journal *Clinical Evidence* (Scott and Kowalczyk, 2006), compared with placebo, intra-articular hyaluronan and hyaluronan derivatives may improve knee pain and function compared with placebo at up to 13 weeks after injection, but may have no longer-term benefits. The review stated that this conclusion is based upon low-quality evidence. The assessment also found that, compared with intra-articular corticosteroids, hyaluronan may be more effective than intra-articular corticosteroids at reducing pain at 5 to 13 weeks, although they may be as effective as each other in the shorter term. According to the review, this conclusion is based upon very low-quality evidence. The assessment also noted that there is no evidence on the effectiveness of subsequent courses of hyaluronan, and if diminishing returns exist.

Kirwan (1997) reviewed 10 clinical trials of hyaluronan of the knee joint. The review found slightly greater benefit from the injections versus placebo at 1 to 6 months after treatment. Of 4 subsequently published randomized controlled trials (RCTs), 3 (Lohmander, 1996; Corrado et al, 1995; Formiguera, 1995) found no significant difference versus placebo at 2 to 5 months after treatment, but both active and placebo groups improved compared with baseline. One of the trials (240 people) included a subgroup analysis of people aged over 60 years with moderate to severe symptoms; these benefited more with active treatment than placebo (Lohmander, 1996). The 4th subsequent RCT, involving 100 people, found significant benefit on a standardized pain assessment tool (the Lequense index) with hyaluronan versus placebo, both at 5 weeks and 4 months (Huskisson, 1999). Another RCT also found a trend toward greater pain relief and functional recovery in patients treated with intra-articular hyaluronan versus placebo injection, but the differences between the 2 groups were not statistically significant (Tamir, 2001).
Bellamy (2002) viewed the evidence comparing viscosupplementation to steroid injections. One RCT reviewed by Bellamy (2002) found a benefit of hyaluronan at 5 and 8 weeks against steroids, but no difference in effect between steroid and hyaluronan injections was found in 2 other RCTs.

An assessment of viscosupplementation for knee OA by the Canadian Agency for Drugs and Technologies in Health (CADTH) (Dagenais, 2006) found that evidence suggests modest short-term reductions in pain and improvements in function, and no superiority among viscosupplement products. Adverse events are rare, benign, temporary, and likely associated with the intra-articular injection. The assessment reported that clinical practice guidelines and evidence suggest that this approach is most suitable for patients with mild to moderate knee OA, and in those for whom other approaches are contraindicated, or have failed.

Guidance from the National Institute for Health and Clinical Excellence (2008) found that the research evidence on the efficacy of viscosupplementation is often difficult to interpret because of confounders including different molecular weights of hyaluronans, different injection schedules (ranging from once-weekly to a series of 5 injections), poor trial design despite large numbers of studies (e.g., lack of intention-to-treat analyses, limitations in blinding). The guidance concludes that the evidence seems to suggest a benefit for reducing pain up to 3 months after a series of 3 to 5 injections, although the effect size is generally small. "Given this, and the cost of the therapies together with increased clinician visits required for injections, there appears to be a poor rationale for routine clinical use." The guidance noted that clinical trials do not suggest subgroups of OA patients who may have greater benefit from viscosupplementation.

An assessment by AETMIS (2007) reached similar conclusions to the NICE guidance. The AETMIS assessment concluded that viscosupplementation offers clinically modest relief from the symptoms of knee OA over a period that could last up to
several weeks. The assessment found viscosupplementation to be a 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. They were also unable to identify patient subgroups more likely to benefit from this treatment compared with other 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 OA 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 systematic evidence review prepared by the BlueCross BlueShield Association Technology Evaluation Center Evidence‐based Practice Center for the Agency for Healthcare Research and Quality (Samson et al, 2007) concluded: "Viscosupplementation trials generally report positive effects on pain and function scores compared to placebo, but the evidence on clinical benefit is uncertain, due to variable trial quality, potential publication bias, and unclear clinical significance of the changes reported."

More recently, the American Academy of Orthopedic Surgeons (2013) concluded that they "cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee." This conclusion was a strong recommendation, and was based on a metaanalysis of studies that failed to show a clinically significant benefit from viscosupplementation. The 2013 AAOS conclusions were more definitive than the previous American Academy of Orthopaedic Surgeons' clinical guideline on the treatment of OA of the knee (2008), which stated that the AAOS cannot recommend for or
against use of intra-articular HA injections.

American College of Rheumatology clinical practice guidelines on osteoarthritis (Hochberg, et al., 2012) conclude that they have no recommendations regarding the use of intraarticular hyaluronates in the knee and hip.

Guidelines on osteoarthritis from the National Institute for Health and Care Excellence (NICE, 2014) state: "Do not offer intra-articular hyaluronan injections for the management of osteoarthritis."

Rutjes et al (2012) evaluated the benefits and risks of viscosupplementation for adults with symptomatic knee osteoarthritis. Databases used were MEDLINE (1966 to January 2012), EMBASE (1980 to January 2012), the Cochrane Central Register of Controlled Trials (1970 to January 2012), and other sources. Randomized trials in any language that compared viscosupplementation with sham or nonintervention control in adults with knee osteoarthritis were selected for analysis. Primary outcomes were pain intensity and flare-ups. Secondary outcomes included function and serious adverse events. Reviewers used duplicate abstractions, assessed study quality, pooled data using a random-effects model, examined funnel plots, and explored heterogeneity using meta-regression. A total of 89 trials involving 12,667 adults met inclusion criteria -- 68 had a sham control, 40 had a follow-up duration greater than 3 months, and 22 used cross-linked forms of hyaluronic acid. Overall, 71 trials (9,617 patients) showed that viscosupplementation moderately reduced pain (effect size, -0.37 [95% CI: -0.46 to -0.28]). There was important between-trial heterogeneity and an asymmetrical funnel plot: Trial size, blinded outcome assessment, and publication status were associated with effect size. Five unpublished trials (1,149 patients) showed an effect size of -0.03 (CI: -0.14 to 0.09). Eighteen large trials with blinded outcome assessment (5,094 patients) showed a clinically irrelevant effect size of -0.11 (CI: -0.18 to -0.04). Six trials (811 patients) showed that viscosupplementation increased, although not statistically
significantly, the risk for flare-ups (relative risk, 1.51 [CI: 0.84 to 2.72]). Fourteen trials (3,667 patients) showed that viscosupplementation increased the risk for serious adverse events (relative risk, 1.41 [CI: 1.02 to 1.97]). The authors concluded that the benefit of viscosupplementation on pain and function in patients with symptomatic osteoarthritis of the knee is minimal or non-existent. Because of increased risk for serious adverse events and local adverse events, the administration of these preparations should be discouraged.

Although some have argued that viscosupplements can avoid the risks of nonsteroidal anti-inflammatory medications and opiates, and delay the need for knee replacement surgery, there is a lack of reliable evidence that viscosupplements reduces the quantity of NSAIDs and opiates, delay disease progression, or reduce knee replacement surgeries.

There is limited evidence of the effectiveness of repeat viscosupplement treatments. Available evidence is limited to uncontrolled case series, so that improvements following repeat treatment may be due to the natural history of the condition and placebo effects. Evidence submitted to the FDA regarding repeat treatment consisted of 2 studies. One study, by Scali et al (1995) was an uncontrolled study of 5 weekly injections of viscosupplementation repeated every 6 months for 30 months, for a total of 25 injections. A second study by Kotz and Kolarz (1999) examined the effectiveness of viscosupplementation in 108 patients, 14 of whom received repeat injections within 4 to 8 months due to pain recurrence, 6 of whom completed 12 month follow-up. Guidance from the National Institute for Health and Clinical Excellence (NICE, 2007) found that the evidence seems to suggest a benefit for reducing pain up to 3 months after a series of 3 to 5 injections, although the effect size is generally small.

In a randomized controlled trial, Juni et al (2007) compared the safety and effectiveness of intra-articular hylan and 2 hyaluronic acids (HAs) in OA of the knee (n = 660). Patients were randomly assigned to receive 1 cycle of 3 intra-articular injections per
knee of 1 of 3 preparations: (i) a high molecular weight cross-linked hylan, (ii) a non-cross-linked medium molecular weight HA of avian origin, or (iii) a non-cross-linked low molecular weight HA of bacterial origin. The primary outcome measure was the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score at 6 months. Secondary outcome measures included local adverse events (effusions or flares) in injected knees. During months 7 to 12, patients were offered a 2nd cycle of viscosupplementation. Pain relief was similar in all 3 groups. The difference in changes between baseline and 6 months between hylan and the combined HAs was 0.1 on the WOMAC pain score (95 % confidence interval [CI]: -0.2 to 0.3). No relevant differences were observed in any of the secondary efficacy outcomes, and stratified analyses provided no evidence for differences in effects across different patient groups. There was a trend toward more local adverse events in the hylan group than in the HA groups during the first cycle (difference 2.2 % [95 % CI: -2.4 to 6.7]), and this trend became more pronounced during the second cycle (difference 6.4 % [95 % CI: 0.6 to 12.2]). The authors concluded that there was no evidence for a difference in effectiveness between hylan and HAs. In view of its higher costs and potential for more local adverse events, these investigators see no rationale for the continued use of hylan in patients with knee OA.

The Galician Agency for Health Technology Assessment (Fernandez Lopez and Ruano-Ravina, 2005) systematically reviewed the evidence for the use of viscosupplementation in hip osteoarthritis. The authors of the systematic review identified seven clinical trials that met the inclusion criteria and one systematic review. The number of patients in the trials ranged from 22 to 104. Five trials had no control group, one compared 2 viscosupplements of different molecular weight, and the remainder compared viscosupplements with administration of intra-articular glucocorticoids and with a group that received placebo. Relief of pain was estimated to be around 40 % to 50 % by most studies, though the duration of this effect post-treatment was not known. The authors
reported that the RCT with 3 arms reported no differences between the treatments at the end of the follow-up period. Moreover, this study displayed the highest quality of all those included. The authors concluded that the absence of a control group in most of the clinical trials means that there is no way of ascertaining the effectiveness of viscosupplements in hip OA. Accordingly, viscosupplements "should not be used outside the ambit of experimental studies until better-quality evidence is available."

In a review on viscosupplementation in the treatment for patients with hip OA, Conrozier and Vignon (2005) concluded that to date, in the absence of placebo-controlled studies, the effectiveness of intra-articular injections of hyaluronic acid or its derivatives in the symptomatic treatment of hip OA cannot be determined conclusively. Nevertheless, the published data suggest that viscosupplementation may be effective. These researchers stated that double-blind, controlled studies are needed to confirm these data, before viscosupplementation should be included into the treatment paradigm for patients with hip OA.

Migliore et al (2006) reported the effects of hylan G-F 20 administered through ultrasound (US)-guided intra-articular (IA) injections in patients with symptomatic hip OA. They treated 30 patients with symptomatic hip OA. Under US guidance, 7 patients received 1 injection, 21 patients had 2 injections, and 2 patients received 3 injections, each with 2 ml of hylan G-F 20. Lequesne index, visual analog scale (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. No systemic adverse events were observed. Lequesne index, VAS pain score, and NSAID consumption showed a reduction that was statistically significant to the baseline. The present observation suggested the potentiality for the safety and effectiveness of hylan G-F 20 injected under US guidance in patients with symptomatic hip OA. The authors stated that further controlled studies are needed.
The Canadian Agency for Drugs and Technologies in Health's report on IA hyaluronic acid for hip OA (Dagenais, 2007) stated that the best available evidence suggests that hyaluronic acid may offer symptomatic relief in patients with mild to moderate hip OA for whom other conservative therapies are contraindicated or have failed. Currently, there is insufficient good quality evidence to determine this conclusively.

van den Bekerom et al (2008) evaluated the effectiveness of viscosupplementation in the treatment of hip OA. A total of 16 articles concerning the effectiveness of a total of 509 patients undergoing viscosupplementation for hip OA were included -- 12 European studies, 3 Turkish studies and 1 American study with levels of evidence ranging from I to IV evaluated the following products: Hylan G-F 20, Hyalgan, Ostenil, Durolane, Fermatron and Orthovisc. Heterogeneity of included studies did not allow pooled analysis of data. The authors noted that despite the relatively low level of evidence of the included studies, viscosupplementation performed under fluoroscopic or ultrasound guidance seems an effective treatment and may be an alternative treatment of hip OA. Intra-articular injection of (derivatives of) hyaluronan (HA) into the hip joint appears to be safe and well-tolerated. However, the authors stated that viscosupplementation cannot be recommended as standard therapy in hip OA for wider populations, and therefore the indications remain a highly individualized matter.

Conrozier et al (2009) assessed the effectiveness and tolerability of a single intra-articular injection of non-animal-stabilized HA (NASHA) in patients treated for symptomatic hip OA (HOA). A total of 40 patients suffering from HOA were treated by a single intra-articular injection of NASHA in the painful hip under fluoroscopy. Patient global assessment (PGA) and walking pain (WP) on a 100-mm VAS, WOMAC index, and Lequesne index were assessed at each visit. Treatment effectiveness was assessed using OMERACT-OARSI response criteria, minimal clinically important improvement (MCII), patient acceptable symptom state (PASS) obtained from PGA,
WOMAC and WP. Predictive factors of effectiveness were also studied. A total of 34 patients were assessable (mean follow-up of 159 days). All clinical variables (WP, PGA, WOMAC, Lequesne index) decreased significantly between baseline and last evaluation. Twenty-two patients (71%) were classified OMERACT-OARSI responders, 25 subjects (75.8%) were classified PASS+, and 19 (61.3%) fulfilled criteria for MCII. Out of clinical and radiological variables only Lequesne index ($p = 0.04$) and WOMAC ($p = 0.04$) at baseline were found to be predictive of treatment effectiveness; the treatment was well-tolerated. There were no severe adverse events related to the treatment or to the procedure. However 15 of the 28 assessable patients experienced transient increase of pain in the target hip during the first week following injection. The authors concluded that viscosupplementation of the hip with NASHA is easily feasible in daily clinical practice, safe and well-tolerated despite a frequent increase of pain the days following injection. Moreover, they stated that prospective, controlled trials are needed to confirm these data and to evaluate both safety and effectiveness of a second course of treatment.

In a pilot study, Salk and colleagues (2005) examined the safety and effectiveness of viscosupplementation with sodium hyaluronate versus phosphate-buffered saline control for pain associated with OA of the ankle. Results of this study suggested that 5 weekly intra-articular injections of sodium hyaluronate in patients who have OA of the ankle are well-tolerated, can provide sustained relief of pain, and improve ankle function. These findings are consistent with previously published studies using intra-articular injections of sodium hyaluronate in other articular joints but require confirmation in a large, randomized, saline-controlled study. These investigators concluded that if confirmed, these findings would provide a valuable non-operative treatment option for patients who have OA of the ankle.

Carpenter and Motley (2008) noted that although anecdotal data exist, no long-term studies regarding the use of viscosupplementation in the ankle have been published to
date. These researchers compared pain reduction following ankle arthroscopy versus that following ankle arthroscopy combined with weekly intra-articular instillation of hylan G-F 20 during the first 3 post-operative weeks. They found that both treatment groups experienced statistically significantly decreased pain following the intervention ($p = 0.002$ and $p = 0.0009$ for the arthroscopy alone and arthroscopy plus hylan groups, respectively), and that those who received 3 intra-articular injections of hylan G-F 20 following ankle arthroscopy improved statistically significantly ($p = 0.0014$) more than did those who underwent arthroscopy as a sole therapy. These preliminary results suggested that viscosupplementation combined with arthroscopy may be more beneficial than arthroscopy alone, and provide further insight into the role of viscosupplementation in the treatment of ankle OA.

van Brakel and Eygendaal (2006) assessed the safety and effectiveness of IA injection of hyaluronic acid in 19 consecutive elbows with post-traumatic OA. In 18 patients (10 male and 8 female patients; mean age of 45.6 years [SD, 15.0 years]), 3 injections of sodium hyaluronate were given within 4 weeks at regular intervals. Evaluation took place just before the first injection, as well as after 3 and 6 months, and consisted of the Elbow Function Assessment Score, the Functional Rating Index of Broberg and Morrey, and the Modified Andrews Elbow Scoring System. Pain was also assessed by means of VAS. Viscosupplementation resulted in slight, short-term pain relief and a very limited decrease in activity impairment at evaluation after 3 months. After 6 months, no beneficial effects were noticed in any of the 19 injected elbows. Other parameters were not influenced by treatment with viscosupplementation at any time. Systemic or local adverse effects did not occur. The authors concluded that because the use of viscosupplementation for the treatment of post-traumatic OA of the elbow provides only slight, short-term pain relief and a very limited decrease in activity impairment and the other parameters were not modified, viscosupplementation is not suitable for this indication.
In a pilot study, Cleary and colleagues (2008) examined the potential effectiveness of HA injection therapy in the treatment of lumbar facet joint arthritis. A total of 13 patients with symptomatic lumbar facet joint arthritis who met the inclusion criteria were prospectively recruited. Pre-treatment evaluation of patients was by questionnaire, including the VAS and Oswestry Disability Questionnaire. A single injection of HA into affected facet joints was then performed, with correct placement confirmed on fluoroscopy. Patients were similarly evaluated 6 weeks after treatment. A total of 18 facets were injected with HA. At 6-week follow-up, there was no significant improvement in pain when measured on the VAS. There was also no significant improvement in the Oswestry Disability Questionnaire. The authors concluded that preliminary results from this pilot study did not demonstrate any benefit of viscosupplementation in the management of symptomatic lumbar facet joint arthropathy.

Grogan and colleagues (2009) noted that in the recent past, non-surgical treatment of OA was limited to rest, immobilization, physical therapy, activity modifications, NSAIDs, analgesics, weight loss, assistive devices for walking, and corticosteroid injections. Viscosupplementation is a welcome addition to the non-surgical armamentarium available to physicians. It is used to introduce hyaluronic acid into the joint to provide initial lubrication and shock absorption, and to change the long-term disease process. These investigators discussed the pathology of OA; the characteristics, physiology, and administration of commercial viscosupplements; and reviewed the research on hyaluronic acid (HA) use in the foot and ankle. They concluded that additional studies are needed to test the safety and effectiveness of this treatment in other parts of the foot. Furthermore, in a review on the use of HA as a treatment for ankle OA, Sun et al (2009) stated that there is only limited published literature relating to the use of HA in the ankle.

Salini et al (2009) evaluated the effectiveness of a single ultrasound-guided injection of HA in patients suffering from
carpo-metacarpal OA (CMC-OA). A total of 18 patients with CMC-OA, grade 2 to 3 Kellgren and Lawrence score were enrolled. They underwent clinical evaluation at baseline and after 1 month follow-up, evaluating: grading of pain (VAS at rest and during activities), function (Dreiser Index), grip and pinch strengths Jamar dynamometer), as well as NSAIDs consumption. Each patient received a single ultrasound-guided injection of HA into the articular CMC joint. The results were that pain at rest and during activities decreased from 1.8 +/- 1.07 to 0.5 +/- 0.68 (p < 0.001) and from 8.05 +/- 0.94 to 4.15 +/- 1.42 (p < 0.001), respectively. Dreiser Functional Index showed a significant improvement (+11.59 %; p < 0.004), as well as pulp pinch strength (24.07 %; p < 0.001). The consumption of NSAIDs was also clearly reduced, from 16 to 7 patients (-45 %) and from 2.45 +/- 1.98 to 1.15 +/- 1.30 tablets per week (p < 0.02). Mild local side effects, lasting less than 3 hours, were observed only in 2 cases. The authors concluded that a single ultrasound-guided injection of HA is a safe and effective procedure in CMC-OA, with a significant improvement in terms of pain and function. However, they stated that studies with larger samples and longer term follow-up are needed.

The American Academy of Orthopedic Surgeons published a clinical practice guideline on the treatment of glenohumeral osteoarthritis in the adult patient population (Izquierdo et al, 2010). Of the 16 recommendations addressed, 9 are inconclusive. Two were reached by consensus -- that physicians use peri-operative mechanical and/or chemical venous thromboembolism prophylaxis for shoulder arthroplasty patients and that total shoulder arthroplasty not be performed in patients with glenohumeral OA who have an irreparable rotator cuff tear. Four options were graded as weak: (i) the use of injectable viscosupplementation; (ii) total shoulder arthroplasty and hemiarthroplasty as treatment; (iii) avoiding shoulder arthroplasty by surgeons who perform fewer than 2 shoulder arthroplasties per year (to reduce the risk of immediate post-operative complications); and (iv) the use of keeled or pegged all-polyethylene cemented glenoid
components. The single moderate-rated recommendation was for the use of total shoulder arthroplasty rather than hemiarthroplasty. The clinical guideline noted that management of glenohumeral osteoarthritis remains controversial; the scientific evidence on this topic can be significantly improved.

In a randomized, double-blind clinical trial, Vanelli and associates (2010) evaluated the safety and effectiveness of intra-articular polynucleotides (PN) gel injections in the treatment of knee OA associated with persistent knee pain. A total of 60 patients were enrolled and randomized to receive intra-articular polynucleotides (n = 30) or hyaluronan (n = 30); patients received 5 weekly intra-articular knee injections and the follow-up period was 3 months after the end of treatment. Primary endpoint was to determine PN efficacy in reducing knee pain at the end of the study over baseline value and over standard HA viscosupplementation. Pain levels were measured using a 0 to 10 cm VAS. Secondary endpoints included knee osteoarthritis outcome score (KOOS), NSAIDs consumption, crackling during movement and articular mobility limitation. The mean global VAS pain decreased from 5.7 +/- 1.9 cm (T0) to 1.9 +/- 1.5 cm (T16) in the PN group and from 4.9 +/- 2.0 cm (T0) to 2.1 +/- 1.4 cm (T16) in the HA group. The reduction in pain was statistically significant for both groups. Increases of KOOS from baseline values were statistically significant in both groups. No significant adverse events were reported. The authors concluded that these findings suggest that intra-articular PN can be a valid alternative to traditional HA supplementation for the treatment of knee OA. These preliminary findings need to be validated by further research.

Migliore et al (2011) evaluated the effectiveness of viscosupplementation treatment of ankle OA in the current literature. The following databases were searched: Medline (period 2006 to 2008), Database of Abstract on Reviews and Effectiveness and Cochrane Database of Systematic Reviews. Reference lists of relevant articles were controlled for additional references. The search terms Review, Viscosupplementation
(VS), Osteoarthritis (OA), Hyaluronic acid (HA), Hyaluronan, Sodium hyaluronate, Ankle OA, Ankle joint were used to identify all studies relating to the use of VS therapy for the ankle OA. Methodological quality of included studies was assessed by assigning level of evidence as previously defined by the Centre for Evidence Based Medicine (CEBM). A total of 7 articles concerning the efficacy of a total of 275 patients undergoing VS treatment for ankle OA were included. One European study, 1 Taiwanese study, 1 Italian study, 1 Turkish study and 3 American studies with level of evidence ranging from I to IV evaluated the following products: Hyalgan, Synvisc, Supartz, Adant. The authors concluded that viscosupplementation is used widely in knee OA and is included in the professional guidelines for treatment of the disease in this joint. The potential for treating OA of the ankle joint by viscosupplementation has been suggested in the literature, however, no dosing studies have been published to date, and dosing in the ankle joint remains an area for discussion. They stated that viscosupplementation could potentially provide an useful alternative in treating such patients with painful ankle OA.

In a randomized placebo-controlled trial, Munteanu and colleagues (2011) evaluated the effectiveness of a single intra-articular injection of hylan G-F 20 (Synvisc) for symptomatic first meta-tarso-phalangeal joint (MTPJ) OA. Participants (n = 151) with symptomatic first MTPJ OA were randomly allocated to receive up to 1 ml intra-articular injection of either hylan G-F 20 or placebo (saline). Participants and assessors were blinded. Outcomes were evaluated at 1, 3 and 6 months after injection. The primary outcome measurement was the foot pain domain of the Foot Health Status Questionnaire (FHSQ) at 3 months. Secondary outcome measurements were foot function assessed via the FHSQ, first MTPJ pain and stiffness, magnitude of symptom change, global satisfaction, health-related quality of life (assessed using the Short-Form-36 version two), first MTPJ dorsiflexion range of motion, hallux plantar flexion strength, use of pain-relieving medication or co-interventions and changes in plantar pressures. No statistically significant
differences in foot pain were found between the groups at 3 months. There were few statistically significant differences in the secondary outcome measures. Overall, the incidence of adverse effects was not significantly different between groups. The authors concluded that an intra-articular injection of hylan G-F 20 is no more effective than a placebo in reducing symptoms in people with symptomatic first MTPJ OA.

The American Physical Therapy Association’s clinical practice guidelines on “Plantar fasciitis” (McPoil et al, 2008) and the American College of Foot and Ankle Surgeons’ clinical practice guideline on “The diagnosis and treatment of heel pain” (Thomas et al, 2010) do not mention the use of hyaluronidase.

The American College of Occupational and Environmental Medicine (ACOEM)’s occupational medicine practice guideline on “Knee disorders” (2011) provided no recommendation on the use hyaluronic acid injections for patellofemoral joint pain because of insufficient evidence.

Stahl et al (2005) stated that trapeziometacarpal (TMC) joint arthritis is a disabling condition presenting with pain at the base of the thumb causing impairment of hand function. Non-operative treatment at an early stage includes intra-articular steroid injection. Although this treatment may bring about prompt symptomatic relief, its effectiveness is unpredictable. There is previous evidence that injection of sodium hyaluronate is safe and effective in the treatment of knee arthritis. These researchers proposed that intra-articular injection of sodium hyaluronate, for the symptomatic treatment of TMC joint arthritis, could provide symptomatic relief without the adverse effects of steroids. A total of 52 patients with TMC joint grade II arthritis were randomized prospectively either for methylprednisolone or hyaluronate intra-articular injections. Initial evaluation included an estimation of pain, grip, pinch strengths and the functional Purdue Pegboard Test (PPT). This evaluation was repeated after 1, 3, and 6 months and statistically compared with the initial evaluation. In both groups, the intra-articular injection produced a relief of pain
after 1 month. Grip strength improved significantly in the group treated by the steroid during the whole evaluation period. The patients treated by hyaluronate showed improvement in grip strength after 6 months and in the pinch and the PPT after 3 months. The authors concluded that steroids and hyaluronate injections were found effective in reducing pain. Hyaluronate was more effective in the improvement of some aspects of fine hand function.

Fuchs et al (2006) performed a prospective assessment of the effectiveness and tolerability of intra-articular sodium hyaluronate (SH; Ostenil mini) and triamcinolone acetonide (TA; Volon A10) for treatment of osteoarthritis (OA) of the carpometacarpal joint (CMCJ) of the thumb in a 26-week, controlled, randomized, on an intention-to-treat, masked-observer study. Patients were treated with 3 intra-articular injections of either SH (n = 28) or TA (n = 28). Primary assessments were pain according to a 100-mm VAS and extensive clinical and functional parameters such as swelling, grip power and range of motion. The population was analyzed using 1- and 2-sided Mann-Whitney (MW) estimators. Maximum pain relief occurred at 2 to 3 weeks for TA and at week 26 for SH after the first intra-articular injection. At weeks 2 to 3 TA was significantly better than SH (MW: 0.3319 and 0.3063; p = 0.9827 and 0.9929). At week 26 a slight superiority of SH could be observed (MW: 0.53; p = 0.3624) and non-inferiority could be proven. After 26 weeks lateral pinch power was significantly better in the SH-group (MW: 0.6331; p = 0.0226). In all, 88.0% of patients treated with SH and 79.1% of the TA-group described pain improvement after 26 weeks. Both agents were well-tolerated. No adverse events with causal connection to the investigational products occurred. The authors concluded that a single course of 3 SH injections is effective in relieving pain and improving joint function in patients with OA of the CMCJ of the thumb. Although in comparison with triamcinolone its effects were achieved more slowly, the results indicated a superior long-lasting effect of hyaluronan at 6 months after end of treatment period.
Roux and colleagues (2007) compared the effectiveness on pain relief and function of 1, 2 or 3 injections of intra-articular hyaluronic acid in symptomatic OA of the CMCJ of the thumb. Among subjects with symptomatic OA of the CMCJ of the thumb referred to the Rheumatology Department of Nice, patients free of any joint injection in last 6 months with pain VAS greater than 40 and with Kellgren and Lawrence score between 2 and 4 were included. Each subject was randomly allocated to receive, at weekly intervals, 1 (group 1), 2 (group 2), or 3 injections (group 3) of 1 ml sodium hyaluronidate (Sinovial). Injections were given under imaging control. Socio-demographic characteristics, VAS and functionality (Dreiser Functional Index) were assessed at baseline, at 1 month and at 3 months. An intention-to-treat analysis was performed. A total of 42 subjects were enrolled in the study. Their mean age was 64.8 (8.0) years; and 90.5 % were women. Baseline pain VAS, and mean Dreiser functional index were 57.7 (17.1) and 12.5 (5.8), respectively. A repeated measure analysis of variance (ANOVA) model was used to compare the time-course profile of the 3 treatment groups for VAS and Dreiser index. Due to statistically significant groups-time interaction the analyses were conducted at each evaluation time. No difference was found for VAS at 1 month (p = 0.075) and 3 months (p = 0.382). Intra-group differences between baseline and 3 months was significant in groups 2 and 3 (p = 0.012 and p = 0.002). The authors concluded that no significant differences were found between each group over the study period for pain relief and function. But the intra-groups analysis results showed that intra-articular sodium hyaluronidate injections into the carpometacarpal joint of the thumb in OA can be effective on pain and function. They stated that what is now needed is a controlled placebo randomized study with larger samples and longer term follow-up of the achieved effects.

In a randomized, open-label, evaluator-blinded clinical study, Bahadir et al (2009) compared the therapeutic effects of sodium hyaluronate and corticosteroid injections on TMC joint OA. This study included 40 women with stage II or III TMC joint osteoarthritis. The steroid group (n = 20) received 1 injection of
20-mg triamcinolone acetonide once and the hyaluronate group (n = 20) received 3 injections of 5-mg sodium hyaluronate at 1-week intervals. The pain level was assessed using a VAS and grip and pinch strengths were measured using a hand grip dynamometer and pinch gauge. The Duruoiz Hand Index was used to evaluate hand function. Pain level decreased significantly over 12 months for the steroid group and over 6 months for the sodium hyaluronate group. Pinch strength did not improve in either group, but grip strength improved significantly in both groups. Hand function improved in both groups but it was only significant in the steroid group. The authors concluded that these findings showed that both intra-articular injection of steroid and sodium hyalurinate are effective in TMC joint osteoarthritis. However the steroid injection was found to be superior to sodium hyaluronate injection in reducing pain and improving hand function.

Saline et al (2009) evaluated the effectiveness of a single ultrasound-guided injection of hyaluronic acid (HA) in patients suffering from OA of the CMCJ. A total of 18 patients with OA of the CMCJ, grade 2-3 Kellgren and Lawrence score, attending the Orthopaedic Department of the University Hospital of Chieti, were enrolled. They underwent clinical evaluation at baseline and after 1 month follow-up, evaluating: grading of pain (VAS at rest and during activities), function (Dreiser Index), grip and pinch strengths Jamar dynamometer), as well as NSAIDs consumption. Each patient received a single ultrasound-guided injection of HA into the articular CMCJ. The results were that pain at rest and during activities decreased from 1.8 +/- 1.07 to 0.5 +/- 0.68 (p < 0.001) and from 8.05 +/- 1.94 to 4.15 +/- 1.42 (p < 0.001), respectively. Dreiser Functional Index showed a significant improvement (+11.59 %; p < 0.004), as well as pulp pinch strength (24.07 %; p < 0.001). The consumption of NSAIDs was also clearly reduced, from 16 to 7 patients (-45 %) and from 2.45 +/- 1.98 to 1.15 +/- 1.30 tablets per week (p < 0.02). Mild local side effects, lasting less than 3 hours, were observed only in 2 cases. The authors concluded that a single ultrasound-guided injection of HA is a safe and effective procedure in the treatment of OA of the
CMCJ, with a significant improvement in terms of pain and function. Moreover, they stated that studies with larger samples and longer term follow-up are needed.

Abate et al (2010) noted that the current therapeutic approaches of OA (e.g., analgesics, non-steroidal anti-inflammatory drugs [NSAIDs], COX-2 inhibitors, steroids) do not delay the OA progression or reverse joint damage. Moreover, they may cause relevant systemic side effects. Hyaluronic acid is a physiologic component of the synovial fluid and is reduced in OA joints. Therefore, intra-articular injection of HA, due to its viscoelastic properties and protective effect on articular cartilage and soft tissue surfaces of joints, can restore the normal articular homoeostasis. These effects are evident when HA is properly administered into the articular space; therefore, the use of "image-guided" infiltration techniques is mandatory. Viscosupplementation, with different HA preparations (low and high molecular weight), can be considered when the patient has not found pain relief from other therapies or is intolerant to analgesics or NSAIDs. A 3 to 5 doses regimen is usually recommended with 1 week interval between each injection. Several studies have shown the effectiveness of HA for the treatment of knee OA, with positive effects on pain, articular function (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC], Lequesne Index [LI], range of motion [ROM]), subjective global assessment and reduction in NSAIDs consumption. In general, the benefit is evident within 3 months and persists in the following 6 to 12 months. The authors stated that encouraging but inconclusive results have also been observed for the treatment of shoulder, CMCJ, hip and ankle OA. They concluded that there is the need of better-designed studies to prove the effectiveness of these medications, in order to rule out a placebo effect.

Colorado Division of Workers’ Compensation’s medical treatment guidelines on “Cumulative trauma conditions” (2010) stated that “There is no evidence that hyaluronate injections are superior to steroid injections for carpometacarpal (CMC) thumb arthritis. They may be tried after 3 months of
conservative therapy, including steroid injections, has failed. At the time of this guidelines writing, Hylan G-F 20 has been FDA-approved for the treatment of pain due to osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics”.

Singhal and Zahid (2002) reported on the case of a 27-year old man who presented with the complaints of recurring attacks of painful inflammation affecting finger joints of both hands for the last year. There were no constitutional features of weight loss, fever, anemia, itching or burning sensation over the joints. It was diagnosed to be a case of palindromic rheumatism clinically and treated with hydroxychloroquine.

Finn et al (2010) stated that palindromic rheumatism is characterized by multiple recurrent episodes of arthritis and peri-arthritis (mono- or oligo-articular) that may last hours or days, disappearing without sequels. These investigators reported a 69-year old male with a history of hypertension and a presumptive diagnosis of gout due to recurrent episodes of arthritis and peri-arthritis in the last 30 years. They involved at least 2 joints, lasted few days and were self-limited. The patient was admitted due to arthritis and peri-arthritis of both wrists, knees, ankles, elbows and hands. He presented with fever (38 to 39 degrees C), intense articular pain and anorexia. With a presumptive diagnosis of palindromic rheumatism and the lack of response to NSAIDs, methylprednisolone 20 mg/od per os was started, with an excellent response.

An UpToDate review on “Clinical features of rheumatoid arthritis” (Venables and Maini, 2013) states that “The onset of RA is episodic in a few patients, with one to several joint areas being affected sequentially for hours to days, with symptom free periods that may last from days to months; an episodic pattern referred to as "palindromic rheumatism". Patients with palindromic rheumatism have similar predisposing genetic risk factors and exhibit a dose effect of carriage of certain HLA alleles, as do patients with a more typical persistent
presentation of RA. The proportion of patients presenting with palindromic rheumatism who progress to develop RA or another well-defined disease varies between studies. In one study of 60 patients with palindromic rheumatism followed over 20 years, 40 (67 percent) developed RA. In another study, among 147 such patients seen in a tertiary referral center, 41 were eventually diagnosed with RA (28 percent) and 4 with other disorders (3 with systemic lupus erythematosus and 1 with Behcet’s disease). In one study, a majority of those with palindromic rheumatism also had anti-citrullinated peptide/protein antibodies (ACPA), a serologic finding that is common in RA. In another study, ACPA were positive in 83 percent of patients who progressed to definite RA. Use of antimalarial drugs may reduce the risk of progression to RA. One retrospective study of 113 such patients found that those who received antimalarials were 20 percent less likely to develop a chronic rheumatic disease”.

There is a lack of evidence to support the use of viscosupplementation for the treatment of palindromic rheumatism.

Devulder (1998) noted that millions of patients with chronic sciatica are still treated with epidural corticosteroids. The efficacy of epidural corticosteroids remains questionable, especially in the chronic failed back surgery syndrome (CFBSS). The affected nerve root sleeve(s) are localized with the help of fluoroscopy and contrast dye. Local anesthetic diluted in 1,500 U hyaluronidase and 40 mg methylprednisolone is injected. Twenty patients with CFBSS, a small retrospective pilot study group, were treated. The success rate was evaluated using a verbal pain rating scale, 1 month and 3 months after the last injection. Initially, 12 patients obtained very good pain relief, sustained for greater than 3 months in 11 patients. In 1 patient, pain returned after 1 month or longer. No complications were observed. The authors concluded that this technique was worthwhile for patients with CFBSS and where epidural fibrosis is suspected to be the pain origin. (This was a small uncontrolled study; its findings were confounded by the
combination use of hyaluronidase and methylprednisolone).

In an open, non-blinded, randomized study, Devulder et al (1999) evaluated outcome in patients with FBSS treated with nerve root sleeve injections. A total of 60 patients with documented fibrosis in fewer than 3 nerve roots were included in this study. After random selection, 20 patients were injected with 1 ml bupivacaine 0.5 % combined with 1,500 units hyaluronidase and 1 ml saline per nerve root sleeve (group A), another 20 were treated with 1 ml bupivacaine 0.5 % combined with 40 mg methylprednisolone solution (Depo Medrol) per nerve root (group B), and a third group was treated with bupivacaine 0.5 % combined with 1,500 units hyaluronidase and 40 mg methylprednisolone solution (group C). The volume of each injection was 2 ml. The injections were given twice at an interval of 1 week. The patients were evaluated on a verbal pain rating scale 1, 3, and 6 months after the second injection. The Kruskal-Wallis test was used to detect statistically significant differences among the 3 groups, and the analysis was refined with the Friedman test. Overall, although injections induced analgesia at 1 month, these effects were reduced at 3- and 6-month follow-ups. No statistical differences were found between the 3 treatment groups (after 1 month, p = 0.71; after 3 months, p = 0.69; after 6 months, p = 0.66). The Friedman test showed a significant decrease in treatment score as a function of time in groups B and C (p = 0.015) but not in group A (p = 0.074). Corticosteroids seem responsible for the last phenomenon. (Again, the findings were confounded by the combination use of hyaluronidase and bupivacaine and/or methylprednisolone).

In a prospective, randomized, double-blind study, Ridenour et al (2001) determined the anesthetic efficacy of a buffered lidocaine with epinephrine solution compared to a combination buffered lidocaine with epinephrine plus hyaluronidase solution in inferior alveolar nerve blocks. A total of 30 subjects randomly received an inferior alveolar nerve block using 1 of the 2 solutions at 2 separate appointments using a repeated-measures design. Mandibular anterior and posterior teeth
were blindly pulp tested at 4-min cycles for 60 mins post-injection. No response from the subject to the maximum output (80 reading) of the pulp tester was used as the criterion for pulpal anesthesia. Anesthesia was considered successful when 2 consecutive readings of 80 were obtained. A post-operative survey was used to measure pain and trismus. The results demonstrated 100% of the subjects had profound lip numbness with both solutions for inferior alveolar nerve blocks. The anesthetic success rates for individual teeth ranged from 20 to 80%. There were no significant differences (p > 0.05) between the 2 solutions. However, the combination lidocaine/hyaluronidase solution resulted in a significant increase in post-operative pain and trismus. It was concluded that adding hyaluronidase to a buffered lidocaine solution with epinephrine did not statistically increase the incidence of pulpal anesthesia in inferior alveolar nerve blocks and, because of its potential tissue-damaging effect, it should not be added to local anesthetic solutions for inferior alveolar nerve blocks.

Also, the American College of Occupational and Environmental Medicine’s clinical guideline on “Hand, wrist, and forearm disorders not including carpal tunnel syndrome” (ACOEM, 2011) does not have a recommendation on the instillation of hyaluronidase into the cystic structure after aspiration because of insufficient evidence.

**Temporomandibular Disorders:**

In a systematic review, Manfredini and colleagues (2010) examined the clinical studies on the use of HA injections to treat temporomandibular joint (TMJ) disorders performed over the last decade. The selected papers were assessed according to a structured reading of articles format, which provided that the study design was methodologically evaluated in relation to 4 main issues: (i) population, (ii) intervention, (iii) comparison, and (iv) outcome. A total of 19 papers were selected for inclusion in the review, 12 dealt with the use of HA in TMJ disk displacements and 7 dealt with inflammatory-degenerative disorders. Only 9 groups of researchers were
involved in the studies, and less than 50% of the studies (8/19) were RCTs. All studies reported a decrease in pain levels independently by the patients’ disorder and by the adopted injection protocol. Positive outcomes were maintained over the follow-up period, which ranged between 15 days and 24 months. The superiority of HA injections was shown only against placebo saline injections, but outcomes are comparable with those achieved with corticosteroid injections or oral appliances. The available literature seems to be inconclusive as to the effectiveness of HA injections with respect to other therapeutic modalities in treating TMJ disorders. The authors concluded that studies with a better methodological design are needed to gain better insight into this issue and to draw clinically useful information on the most suitable protocols for each different TMJ disorder.

Goiato and colleagues (2016) examined if intra-articular injections of HA are better than other drugs used in TMJ arthrocentesis, for the improvement of temporo-mandibular disorder (TMD) symptoms. Two independent reviewers performed an electronic search of the Medline and Web of Science databases for relevant studies published in English up to March 2016. The key words used included a combination of “hyaluronic acid”, “viscosupplementation”, “intra-articular injections”, “corticosteroids”, or “non-steroidal anti-inflammatory agents” with “temporomandibular disorder”. Selected studies were randomized clinical trials and prospective or retrospective studies that primarily investigated the application of HA injections compared to other intra-articular medications for the treatment of TMD. The initial screening yielded 523 articles. After evaluation of the titles and abstracts, 8 were selected. Full texts of these articles were accessed and all fulfilled the inclusion criteria. The authors concluded that intra-articular injections of HA are beneficial in improving the pain and/or functional symptoms of TMDs. However, other drug therapies, such as corticosteroid and NSAIDs injections, can be used with satisfactory results. Moreover, they stated that well-designed clinical studies are needed to identify an adequate protocol, the number of sessions needed, and the
appropriate molecular weight of HA for use.

*Following Anterior Cruciate Ligament Reconstruction:*

In a double-blind, RCT, Di Martino and associates (2016) evaluated pain control and functional recovery provided by a single injection of HA performed the day after anterior cruciate ligament (ACL) reconstruction. The study enrolled 60 patients affected by primary, chronic, and symptomatic ACL tear requiring surgical reconstruction. All patients were treated with the same reconstructive technique and rehabilitation protocol. Exclusion criteria were (i) concurrent articular lesion requiring surgical treatment, (ii) axial mal-alignment in the index limb, and (iii) functional limitation or pain in the contralateral knee. The day after the procedure, the patients were randomized to receive a single injection of 3 mL HA or 3 ml saline solution after surgical drains were removed. All patients were evaluated at baseline and at 15, 30, 60, and 180 days and 12 months after surgery by use of the following tools: Short Form-36 Health Survey (SF-36), International Knee Documentation Committee (IKDC) subjective score, VAS for pain, VAS for general health status, and Tegner score. At each follow-up evaluation, the trans-patellar circumference and active and passive ROM of both knees were recorded. No severe adverse events (AEs) were documented after early viscosupplementation. A significant improvement was documented in both treatment groups. Significant differences were documented in the trans-patellar circumference at 60 days and in active ROM at 30 days post-operatively; patients who received HA had better values compared with the placebo group (p = 0.022 and 0.027, respectively). No statistically relevant intergroup differences were found in the clinical scores. The authors concluded that the findings of this study documented no AEs and had some positive findings in terms of active ROM recovery and trans-patellar circumference reduction. However, the early post-operative application of viscosupplementation did not lead to significant improvement in clinical scores after ACL reconstruction.
Filardo and colleagues (2016) stated that the management of the post-operative period after knee arthroscopic surgery may be challenging because surgical trauma deeply alters the joint microenvironment, causing the release of several catabolic molecules and pro-inflammatory factors that might slow down functional recovery. The possibility of using HA to promote post-operative pain relief and expedite functional improvement appears attractive, considering its biological properties. In a RCT, these researchers evaluated the effects, in terms of pain control and functional recovery, provided by a single HA injection performed at the end of arthroscopic meniscectomy. A total of 90 patients, 18 to 55 years of age, were included according to the following criteria: (i) chronic, symptomatic meniscal tears requiring partial resection; (ii) a healthy contralateral knee; (iii) no previous surgery on the index knee; and (iv) no other concurrent articular lesions requiring surgical treatment (e.g., cartilage or ligament injuries). Patients were randomized into 2 treatment groups: one underwent meniscectomy alone, whereas the other also received an injection of 3 ml HA at the end of the procedure. All patients were evaluated at baseline and then at 15, 30, 60, and 180 days using the following tools: IKDC subjective, KOOS, VAS for pain, VAS for general health status, and Tegner scores. The trans-patellar circumference and active and passive ROM were also recorded during the follow-up evaluations. No major AEs were reported using HA post-operatively. A statistically significant increase in all the clinical scores was reported in both treatment groups, but no significant intergroup difference was documented at any follow-up evaluation. No difference was observed also in the objective measurements. The mean time to return to full sports activity was not different between groups, and a comparable satisfaction rate was recorded in both treatment groups. The authors concluded that early post-operative viscosupplementation did not provide significant clinical benefits after arthroscopic meniscectomy. They stated that despite the lack of major AEs, the administration of a single HA injection at the end of the surgical procedure is not a
successful strategy to provide either faster functional recovery or symptomatic improvement after meniscectomy.

**Hemophilic Arthropathy:**

de Rezende and co-workers (2015) examined if joint lavage, viscosupplementation and triamcinolone improve joint pain, function and quality of life in patients with severe hemophilic arthropathy. A total of 14 patients with knee and/or ankle hemophilic arthritis with and without involvement of other joints underwent joint lavage and subsequent injection of hylan G-F20 and triamcinolone in all affected joints. Patients answered algo-functional questionnaires (Lequesne and WOMAC), VAS for pain and SF-36 pre-operatively, and at 1, 3, 6 and 12 months post-operatively; 16 knees, 15 ankles, 8 elbows and 1 shoulder were treated in 14 patients; 6 patients had musculoskeletal bleeding [ankle (n = 1), leg muscle (n = 2) and knees (n = 4)] at 3 months affecting the results. Pain did not improve significantly. Function improved (WOMAC, p = 0.02; and Lequesne, p = 0.01). The physical component of SF-36 improved at all time-points except at 3 months, with best results at 1-year follow-up (baseline = 33.4; 1 month = 39.6; 3 months= 37.6; 6 months 39.6 and 1 year = 44.6; p < 0.001). The authors concluded that joint lavage followed by injection of triamcinolone and hylan G-F20 improved function and quality of life progressively up to 1 year, even in severe hemophilic arthropathy. Level of Evidence = IV. This was a small (n = 14) case-series study, and its findings were confounded by the combinational use of joint lavage, viscosupplementation of HA and triamcinolone.

**Fluoroscopic Guidance for Knee Injections:**

Maricar, et al. (2013) undertook a systematic review to determine the accuracy of intra-articular knee injection (IAKI) and whether this varied by site, use of image-guidance, and experience of injectors, and whether accuracy of injection, site, or use of image-guidance influenced outcomes following IAKIs. Medline, Embase, AMED, CINAHL, Web of Knowledge,
Cochrane Central Registers for Controlled Trials up to Dec 2012 were searched for studies that evaluated either accuracy of IAIs or outcomes related to accuracy, knee injection sites, or use of image-guidance. Within-study and between-study analyses were performed. Data from 23 publications were included. Within-study analyses suggested IAIs at the superomedial patellar, medial midpatellar (MMP), superolateral patellar (SLP) and lateral suprapatellar bursae sites were more accurate when using image-guidance than when blinded (ranges of pooled risk difference 0.09–0.19). Pooling data across studies suggested blinded IAIs at the SLP site were most accurate (87%) while MMP (64%) and anterolateral joint line (ALJL) sites were (70%) least accurate. Overall about one in five blinded IAIs were inaccurate. The authors noted that there was some evidence that experience of the injector was linked with improved accuracy for blinded though not image-guided injections. Based on a small number of studies, short but not longer-term outcomes for ultrasound-guided were found to be superior to blinded IAIs. The authors concluded that image-guided IAIs are modestly more accurate than blinded IAIs especially at the MMP and ALJL sites. Blinded injections at SLP site had good accuracy especially if performed by experienced injectors. The authors stated that further studies are required to address the question whether accurate localization is linked with an improved response.

Telikicherla and Kamath (2016) performed a study to know the correct placement of needle inside the knee joint prior to viscosupplementation by fluoroscopy using a contrast material. The accurate placement of needle was evaluated in a prospective series of 94 consecutive injections in patients without clinical knee effusion. All the injections were performed by single orthopaedic surgeon using a 5 cm 21-gauge needle through anterolateral, and lateral midpatellar portals. The needle placement in the knee joint was confirmed with fluoroscopy using the contrast material. The investigators reported that the accuracy rates through lateral midpatellar and anterolateral portals were lower than expected rate (100%). A total of 43 out of 47 injections were intra-articular, indicating
accuracy of 91.5% through lateral midpatellar portal, 41 out of 47 injections were intra-articular through anterolateral portal with accuracy of 87.4%. The investigators concluded that this study showed that the accuracy of needle placement was higher through lateral midpatellar than the anterolateral portal. A major limitation of this study is that it reported results from a single surgeon, raising questions about the generalizability of the findings. More importantly, the study examined the comparative accuracy of different approaches, and did not examine whether clinical outcomes were improved by use of arthrography.

Appendix

Table: Viscosupplementation Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durolane (hyaluronic acid)</td>
<td>3 ml one time injection</td>
</tr>
<tr>
<td>Euflexxa (1% sodium hyaluronate)</td>
<td>20 mg once a week (1 week apart) for a total of 3 injections.</td>
</tr>
<tr>
<td>Gelsyn-3 (0.84% sodium hyaluronate)</td>
<td>16.8 mg once a week (1 week apart) for a total of 3 injections</td>
</tr>
<tr>
<td>GenVisc 850 (sodium hyaluronate)</td>
<td>25 mg once a week (1 week apart) for a total of 5 injections</td>
</tr>
<tr>
<td>Hyalgan (sodium hyaluronate)</td>
<td>20 mg once a week (1 week apart) for a total of 5 injections</td>
</tr>
<tr>
<td>Hymovis (high molecular weight hyaluronan)</td>
<td>24 mg (3 ml) once a week (1 week apart) for a total of 2 injections</td>
</tr>
<tr>
<td>Monovisc (high molecular weight hyaluronan)</td>
<td>88 mg (4 ml) one time injection</td>
</tr>
</tbody>
</table>
Orthovisc (high molecular weight hyaluronan) 30 mg once a week (1 week apart) for a total of 3 to 4 injections.

Supartz (sodium hyaluronate) 10 mg once a week (1 week apart) for a total of 5 injections.

Synvisc One (Hylan G-F 20) 48 mg one time injection.

Synvisc (Hylan G-F 20) 16 mg once a week (1 week apart) for a total of 3 injections.

Gel-One (Cross-linked Hyaluronate) 30 mg (3 ml) one time injection.

Sources: Prescribing information.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>20610</td>
<td>Arthrocentesis, aspiration and/or injection, major joint or bursa (eg, shoulder, hip, knee, subacromial bursa); without ultrasound guidance</td>
</tr>
</tbody>
</table>

CPT codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>20600</td>
<td>Arthrocentesis, aspiration and/or injection, small joint or bursa (eg, fingers, toes); without ultrasound guidance</td>
</tr>
<tr>
<td>20604</td>
<td>with ultrasound guidance, with permanent recording and reporting</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>20605</td>
<td>Arthrocentesis, aspiration and/or injection, intermediate joint or bursa (e.g., temporomandibular, acromioclavicular, wrist, elbow or ankle, olecranon bursa); without ultrasound guidance</td>
</tr>
<tr>
<td>20606</td>
<td>with ultrasound guidance, with permanent recording and reporting</td>
</tr>
<tr>
<td>20611</td>
<td>Arthrocentesis, aspiration and/or injection, major joint or bursa (e.g., shoulder, hip, knee, subacromial bursa); with ultrasound guidance</td>
</tr>
<tr>
<td>27370</td>
<td>Injection of contrast for knee arthrography</td>
</tr>
<tr>
<td>73580</td>
<td>Radiologic examination, knee, arthrography, radiological supervision and interpretation</td>
</tr>
<tr>
<td>76942</td>
<td>Ultrasonic guidance for needle placement (e.g., biopsy, aspiration, injection, localization device), imaging supervision and interpretation. [not covered for viscosupplementation injection]</td>
</tr>
<tr>
<td>76998</td>
<td>Ultrasonic guidance, intraoperative</td>
</tr>
<tr>
<td>77002</td>
<td>Fluoroscopic guidance for needle placement (e.g., biopsy, aspiration, injection, localization device) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>77003</td>
<td>Fluoroscopic guidance and localization of needle or catheter tip for spine or paraspinous diagnostic or therapeutic injection procedures (epidural or subarachnoid) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>93970</td>
<td>Duplex scan of extremity veins including responses to compression and other maneuvers; complete bilateral study</td>
</tr>
</tbody>
</table>

**Other CPT codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>27445</td>
<td>Arthroplasty, knee, hinge prosthesis</td>
</tr>
<tr>
<td>27446</td>
<td>Arthroplasty, knee, condyle and plateau; medial OR lateral compartment</td>
</tr>
<tr>
<td>27447</td>
<td>Arthroplasty, knee, condyle and plateau; medial AND lateral compartments with or without patella resurfacing</td>
</tr>
<tr>
<td>29880</td>
<td>Arthroscopy, knee, surgical; with meniscectomy (medial AND lateral, including any meniscal shaving) including debridement/shaving of articular cartilage (chondroplasty), same or separate compartment(s), when performed</td>
</tr>
<tr>
<td>29881</td>
<td>Arthroscopy, knee, surgical; with meniscectomy (medial OR lateral, including any meniscal shaving) including debridement/shaving of articular cartilage (chondroplasty), same or separate compartment(s), when performed</td>
</tr>
<tr>
<td>29888</td>
<td>Arthroscopically aided anterior cruciate ligament repair/augmentation or reconstruction</td>
</tr>
</tbody>
</table>

**HCPCS codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7320</td>
<td>Hyaluronan or derivitive, genvisc 850, for hyphen intra-articular injection, 1 mg</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>J7321</td>
<td>Hyaluronan or derivative, Hyalgan or Supartz, hyphen for intra-articular hyphen injection, per dose [knee only - see selection criteria]</td>
</tr>
<tr>
<td>J7322</td>
<td>Hyaluronan or derivative, hymovis, for intra-articular injection, 1 mg</td>
</tr>
<tr>
<td>J7323</td>
<td>Hyaluronan or derivative, Euflexxa, for intra-articular injection, hyphen per dose [knee only - see selection criteria]</td>
</tr>
<tr>
<td>J7324</td>
<td>Hyaluronan or derivative, Orthovisc, for intra-articular injection, per dose [knee only - see selection criteria]</td>
</tr>
<tr>
<td>J7325</td>
<td>Hyaluronan or derivative, Synvisc, or Synvisc-One for intra-articular injection, 1 mg [knee only - see selection criteria]</td>
</tr>
<tr>
<td>J7326</td>
<td>Hyaluronan or derivative, Gel-One, for intra-articular injection, per dose</td>
</tr>
<tr>
<td>J7327</td>
<td>Hyaluronan or derivative, Monovisc, for intra-articular injection, per dose</td>
</tr>
<tr>
<td>J7328</td>
<td>Hyaluronan or derivative, for intra-articular injection, 0.1 mg [Gel-Syn]</td>
</tr>
</tbody>
</table>

**Other HCPCS codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1130</td>
<td>Injection, diclofenac sodium, 0.5 mg</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td><strong>ICD-10 codes covered if selection criteria are met:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>M17.0</td>
<td>Osteoarthritis of knee [not covered for viscosupplementation injection for patellofemoral arthritis]</td>
</tr>
<tr>
<td>M17.32</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>M17.4</td>
<td>Other bilateral or unilateral secondary osteoarthritis of knee [not covered for viscosupplementation injection for patellofemoral arthritis]</td>
</tr>
<tr>
<td>M17.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>M17.9</td>
<td>Osteoarthritis of knee, unspecified [not covered for viscosupplementation injection for patellofemoral arthritis]</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>G57.60</td>
<td>Lesion of plantar nerve [entrapment syndrome]</td>
</tr>
<tr>
<td>G57.63</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>L40.50</td>
<td>Arthropathic psoriasis</td>
</tr>
<tr>
<td>L40.59</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>M12.30</td>
<td>Palindromic rheumatism</td>
</tr>
<tr>
<td>M12.39</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>M15.0 - M16.9</td>
<td>Osteoarthrosis and allied disorders [joints other than knee]</td>
</tr>
<tr>
<td>M18.0 - M19.93</td>
<td></td>
</tr>
<tr>
<td>M22.40 - M22.42</td>
<td>Chondromalacia patellae</td>
</tr>
<tr>
<td>M25.561 - M25.569</td>
<td>Pain in knee</td>
</tr>
<tr>
<td>M26.601 - M26.69</td>
<td>Temporomandibular joint disorders</td>
</tr>
<tr>
<td>M36.2</td>
<td>Hemophilic arthropathy</td>
</tr>
<tr>
<td>M79.2</td>
<td>Neuralgia and neuritis, unspecified [peripheral nerve pain]</td>
</tr>
<tr>
<td>M93.20 - M93.29</td>
<td>Osteochondritis dissecans</td>
</tr>
</tbody>
</table>

ICD-10 codes contraindicated for this CPB (not all-inclusive):
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
</table>
| D65 - D68.4  
D68.8 - D68.9 | Coagulation defects [bleeding disorder]               |
| L08.9    | Local infection of the skin and subcutaneous tissue, unspecified [skin infections at the injection site] |
| M00.00 -  
M01.x9  
M02.10 -  
M02.19  
M02.30 -  
M02.39  
M02.80 -  
M02.89  
M35.2    | Arthropathy associated with infections [active joint infection] |

The above policy is based on the following references:


10. Corrado EM, Peluso GF, Gigliotti S. The effects of intra-articular administration of hyaluronic acid on osteoarthritis of the knee: A clinical study with immunological and...


46. Dagenais S. Intra-articular hyaluronic acid (viscosupplementation) for knee osteoarthritis. Issues in Emerging Health Technologies Issue 94. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); 2006.


65. Sun SF, Chou YJ, Hsu CW, Chen WL. Hyaluronic acid as a


73. Anika Therapeutics, Inc. Orthovisc high molecular weight


91. Stahl S, Karsh-Zafrir I, Ratzon N, Rosenberg N. Comparison of intraarticular injection of depot corticosteroid and hyaluronic acid for treatment of degenerative


100. Venable PJW, Maini RN. Clinical features of rheumatoid arthritis. UpToDate [online serial]. Waltham, MA:


103. Fidia Pharma USA Inc. Hymovis (hyaluronic acid) Prescribing Information. Parsippany, NJ; Fida Pharma USA; October 2015.


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Amendment to
Aetna Clinical Policy Bulletin Number: 0179 Viscosupplementation

All requests for Pennsylvania Medical Assistance recipients will be reviewed according to the approved Aetna Pharmacy benefit prior authorization guidelines.