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Viscosupplementation

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

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Table Of Contents

Policy History

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04/09/2025
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Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

Brand Selection for Medically Necessary Indications for Commercial Medical Plans

As defined in Aetna commercial policies, health care services are not medically necessary when they are more costly than alternative services that are at least as likely to produce equivalent therapeutic or diagnostic results. Durolane, Euflexxa, Gel-One, Gelsyn-3, GenVisc 850, Hyalgan, Hymovis, Supartz FX, Synojoynt, Synvisc, Triluron, Trivisc, and Visco-3 viscosupplement products are more costly to Aetna than other viscosupplement products for medically necessary indications. There is a lack of reliable evidence that Durolane, Euflexxa, Gel-One, Gelsyn-3, GenVisc 850, Hyalgan, Hymovis, Supartz FX, Synojoynt, Synvisc, Triluron, Trivisc, and Visco-3 are superior to the lower cost

viscosupplement products: Monovisc, Orthovisc, and Synvisc One. Therefore, Aetna considers Durolane, Euflexxa, Gel-One, Gelsyn-3, GenVisc 850, Hyalgan, Hymovis, Supartz FX, Synojoynt, Synvisc, Triluron, Trivisc, and Visco-3 to be medically necessary only for members who have a contraindication or intolerance to the available equivalent alternative viscosupplement products: Monovisc, Orthovisc, and Synvisc One.

Policy

Scope of Policy

This Clinical Policy Bulletin addresses viscosupplement (hyaluronate) products for commercial medical plans, and ancillary services. For Medicare criteria for viscosupplementation, see Medicare Part B Criteria (https://www.aetna.com/health-care-professionals/medicare/part-b-step.html).

Note: Requires Precertification:

Precertification of viscosupplementation products are required of all Aetna participating providers and members in applicable plan designs. For precertification of viscosupplementation products, call (866) 752-7021 or fax (888) 267-3277. For Statement of Medical Necessity (SMN) precertification forms, see Specialty Pharmacy Precertification (https://www.aetna.com/health-care-professionals/health-care-professional-forms.html).

I. Criteria for Initial Approval

Aetna considers viscosupplementation (hyaluronates) medically necessary for the treatment of osteoarthritis (OA) in the knee when *all* of the following criteria are met:

A. The diagnosis is supported by radiographic evidence of osteoarthritis of the knee (e.g., as joint space narrowing, subchondral sclerosis, osteophytes and sub-chondral cysts) or the member has at least 5 of the following signs and symptoms:

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/mm^3); *and*

B. The member has knee pain which interferes with functional activities (e.g., ambulation, prolonged standing); *and*

C. The member has experienced an inadequate response or adverse effects with non-pharmacologic treatment options (e.g., physical therapy, regular exercise, insoles, knee bracing, weight reduction); *and*

D. The member has experienced an inadequate response or intolerance or has a contraindication to a trial of an analgesic (e.g., acetaminophen up to 3 to 4 grams per day, non-steroidal anti-inflammatory drugs [NSAIDs], topical capsaicin cream) for at least 3 months; *and*

E. The member has experienced an inadequate response or intolerance or has a contraindication to a trial of intraarticular steroid injections for at least 3 months; *and*

F. The member is not scheduled to undergo a total knee replacement within 6 months of starting treatment.

Aetna considers all other indications as experimental, investigational, or unproven.

II. Continuation of Therapy

Aetna considers continuation of viscosupplement therapy medically necessary for treatment of osteoarthritis in knee when *all* of the following criteria are met:

A. Member meets all initial medical necessity criteria; *and*
B. Member has experienced improvement in pain and functional capacity following the previous injections; *and*
C. At least 6 months has elapsed since the last injection in the prior completed series of injections.

For the use of extended-release triamcinolone acetonide injectable suspension (Zilretta) in the treatment of knee osteoarthritis, see CPB 0673 - Osteoarthritis of the Knee: Selected Treatments (../600_699/0673.html).

Dosage and Administration

Below includes a brief overview of the FDA-approved dosing recommendations for treatment of osteoarthritis (OA) in the knee. For additional dosing and administration information for any of the products listed below, refer to the medication's FDA-approved Prescribing Information.

Table: Viscosupplementation Dosing

Drug	Dose
Durolane (hyaluronic acid)	3 mL one time injection
Euflexxa (1% sodium hyaluronate)	20 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
Gelsyn-3 (0.84% sodium hyaluronate)	16.8 mg once a week (1 week apart) for a total of 3 injections

GenVisc 850 (sodium hyaluronate)	25 mg once a week (1 week apart) for a total of 5 injections
Hyalgan (sodium hyaluronate)	20 mg (2 mL) once a week (1 week apart) for a total of 5 injections
Hymovis (high molecular weight hyaluronan)	Supplied in a 5 mL syringe containing a 3 mL dose of Hymovis to be injected once a week (1 week apart) for a total of 2 injections
Monovisc (high molecular weight hyaluronan)	88 mg (4 mL) one time injection
Orthovisc (high molecular weight hyaluronan)	30 mg once a week (1 week apart) for a total of 3 to 4 injections
Supartz FX (sodium hyaluronate)	25 mg / 2.5 mL prefilled syringe once a week (1 week apart) for a total of 5 injections
Synojoynt (sodium hyaluronate)	20 mg (2 mL) once a week for three weeks for at total of 3 injections
Synvisc (Hylan G-F 20)	16 mg (2 mL) once a week (1 week apart) for a total of 3 injections
Synvisc One (Hylan G-F 20)	48 mg (10 mL); administered as a single intra-articular injection
Triluron (sodium hyaluronate)	20 mg (2 mL) once a week for three weeks for a total of 3 injections
TriVisc (sodium hyaluronate)	2.5 mL intra-articular injection once a week for 3 weeks (1 week apart) for a total of 3 injections
Visco-3 (sodium hyaluronate)	2.5 mL intra-articular injection once a week for 3 weeks (1 week apart) for a total of 3 injections

Sources: Prescribing information

Experimental, Investigational, or Unproven

I. Aetna considers the following as experimental, investigational, or unproven because the effectiveness of these approaches has not

been established in improving health outcomes:

A. Intra-articular polynucleotides in the treatment of knee osteoarthritis
B. Ultrasound guidance, fluoroscopic guidance and knee arthrography for viscosupplement injections
C. Viscosupplementation in combination with anesthetics, corticosteroids, mannitol/sorbitol, mesenchymal stem cells, or platelet rich plasma because the effectiveness of these combinations has not been established. Note: Administration of local anesthetic to anesthetize the injection site for viscosupplementation is considered medically necessary.
D. Amobarbital / hyaluronic acid hydrogel for post-traumatic osteoarthritis (OA) prevention
E. Intra-articular injection of an hexadecylamide derivative of hyaluronic acid for the treatment of femoro-acetabular impingement
F. Viscoelastic hydrogel Hymovis MO.RE for the treatment of knee OA

II. Aetna considers viscosupplementation experimental, investigational, or unproven for the following indications (not an all-inclusive list) because the effectiveness of viscosupplementation for these indications has not been established:

- Chondromalacia patellae
- Facet joint arthropathy
- Following anterior cruciate ligament reconstruction
- Following arthroscopic knee surgery/partial meniscectomy
- For use in joints other than the knee (e.g., ankle, carpo-metacarpal joint, elbow, hip, metatarso-phalangeal joint, shoulder, thumb, and temporomandibular joint)
- Hemophilic arthropathy
- Meniscectomy
- Muscle stiffness
- Osteochondritis dissecans
- Palendromic rheumatism
- Partial or total knee arthroplasty
- Patellofemoral arthritis
- Patellofemoral syndrome (patellar knee pain)

- Peripheral nerve pain
- Plantar nerve entrapment syndrome
- Psoriatic arthritis
- Spastic hemiparesis
- Treatment of first metatarsophalangeal osteoarthritis (hallux rigidus).

CPT Codes / HCPCS Codes / ICD10 Codes

CPT codes covered if selection criteria are met:

Code	Code Description
Combined ozone gas and viscosupplementation - No specific code:	
20610	Arthrocentesis, aspiration and/or injection, major joint or bursa (eg, shoulder, hip, knee, subacromial bursa); without ultrasound guidance
CPT codes not covered for indications listed in the CPB:	
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed
20600	Arthrocentesis, aspiration and/or injection, small joint or bursa (eg, fingers, toes); without ultrasound guidance
20604	with ultrasound guidance, with permanent recording and reporting
20605	Arthrocentesis, aspiration and/or injection, intermediate joint or bursa (eg, temporomandibular, acromioclavicular, wrist, elbow or ankle, olecranon bursa); without ultrasound guidance
20606	with ultrasound guidance, with permanent recording and reporting
20611	Arthrocentesis, aspiration and/or injection, major joint or bursa (eg, shoulder, hip, knee, subacromial bursa); with ultrasound guidance
27369	Injection procedure for contrast knee arthrography or contrast enhanced CT/MRI knee arthrography

Code	Code Description
73580	Radiologic examination, knee, arthrography, radiological supervision and interpretation
76942	Ultrasonic guidance for needle placement(eg, biopsy, aspiration, injection, localization device), imaging supervision and interpretation.[not covered for viscosupplementation injection]
76998	Ultrasonic guidance, intraoperative
77002	Fluoroscopic guidance for needle placement (eg, biopsy, aspiration, injection, localization device) (List separately in addition to code for primary procedure)
77003	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)
93970	Duplex scan of extremity veins including responses to compression and other maneuvers; complete bilateral study
Other CPT codes related to the CPB:	
27445	Arthroplasty, knee, hinge prosthesis
27446	Arthroplasty, knee, condyle and plateau; medial OR lateral compartment
27447	medial AND lateral compartments with or without patella resurfacing
29866	Arthroscopy, knee, surgical; osteochondral autograft(s) (eg, mosaicplasty) (includes harvesting of the autograft
29867	osteochondral allograft (eg, mosaicplasty)
29868	meniscal transplantation (includes arthrotomy for meniscal insertion), medial or lateral
29870	Arthroscopy, knee, diagnostic, with or without synovial biopsy (separate procedure)
29871	for infection, lavage and drainage
29873	with lateral release

Code	Code Description
29874	for removal of loose body or foreign body (eg, osteochondritis dissecans fragmentation, chondral fragmentation)
29875	synovectomy, limited (eg, plica or shelf resection) (separate procedure)
29876	synovectomy, major, 2 or more compartments (eg, medial or lateral)
29877	debridement/shaving of articular cartilage (chondroplasty)
29879	abrasion arthroplasty (includes chondroplasty where necessary) or multiple drilling or microfracture
29880	with meniscectomy (medial AND lateral, including any meniscal shaving) including debridement/shaving of articular cartilage (chondroplasty), same or separate compartment(s), when performed
29881	with meniscectomy (medial OR lateral, including any meniscal shaving) including debridement/shaving of articular cartilage (chondroplasty), same or separate compartment(s), when performed
29883	with meniscus repair (medial AND lateral)
29884	with lysis of adhesions, with or without manipulation (separate procedure)
29885	drilling for osteochondritis dissecans with bone grafting, with or without internal fixation (including debridement of base of lesion)
29886	drilling for intact osteochondritis dissecans lesion
29887	drilling for intact osteochondritis dissecans lesion with internal fixation
29888	Arthroscopically aided anterior cruciate ligament repair/augmentation or reconstruction
HCPCS codes covered if selection criteria are met:	
Generic sodium hyaluronate 1% (Teva), hexadecylamide derivative of hyaluronic acid - no specific code:	
J7318	Hyaluronan or derivative, durolane, for intra-articular injection, 1 mg

Code	Code Description
J7320	Hyaluronan or derivitive, genvisc 850, for intra-articular injection, 1 mg
J7321	Hyaluronan or derivative, hyalgan, supartz or visco-3, for intra-articular injection, per dose
J7322	Hyaluronan or derivative, hymovis, for intra-articular injection, 1 mg
J7323	Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose
J7324	Hyaluronan or derivative, Orthovisc, for intra-articular injection, per dose
J7325	Hyaluronan or derivative, Synvisc, or Synvisc-One for intra-articular injection, 1 mg
J7326	Hyaluronan or derivative, Gel-One, for intra-articular injection, per dose
J7327	Hyaluronan or derivative, Monovisc, for intra-articular injection, per dose
J7328	Hyaluronan or derivative, for intra-articular injection, 0.1 mg [Gel-Syn]
J7329	Hyaluronan or derivative, Trivisc, for intra-articular injection, 1 mg
J7331	Hyaluronan or derivative, synojoynt, for intra-articular injection, 1 mg
J7332	Hyaluronan or derivative, triluron, for intra-articular injection, 1 mg
HCPCS codes not covered for indications listed in the CPB:	
Sorbitol, viscoelastic hydrogel Hymovis MO.RE – no specific code:	
J0300	Injection, amobarbital, up to 125 mg
J0665	Injection, bupivicaine, not otherwise specified, 0.5 mg
J0702	Injection, betamethasone acetate 3 mg and betamethasone sodium phosphate 3 mg [not covered if used with viscosupplement]
J1020	Injection, methylprednisolone acetate, 20 mg [not covered if used with viscosupplement]

Code	Code Description
J1030	Injection, methylprednisolone acetate, 40 mg [not covered if used with viscosupplement]
J1040	Injection, methylprednisolone acetate, 80 mg [not covered if used with viscosupplement]
J1094	Injection, dexamethasone acetate, 1 mg [not covered if used with viscosupplement]
J1100	Injection, dexamethasone sodium phosphate, 1 mg [not covered if used with viscosupplement]
J1700	Injection, hydrocortisone acetate, up to 25 mg [not covered if used with viscosupplement]
J1710	Injection, hydrocortisone sodium phosphate, up to 50 mg [not covered if used with viscosupplement]
J1720	Injection, hydrocortisone sodium succinate, up to 100 mg [not covered if used with viscosupplement]
J2001	Injection, lidocaine hcl for intravenous infusion, 10 mg [not covered if used with viscosupplement]
J2150	Injection, mannitol, 25% in 50 ml
J2650	Injection, prednisolone acetate, up to 1 ml [not covered if used with viscosupplement]
J2920	Injection, methylprednisolone sodium succinate, up to 40 mg [not covered if used with viscosupplement]
J2930	Injection, methylprednisolone sodium succinate, up to 125 mg [not covered if used with viscosupplement]
J3300	Injection, triamcinolone acetonide, preservative free, 1 mg [not covered if used with viscosupplement]
J3301	Injection, triamcinolone acetonide, not otherwise specified, 10 mg [not covered if used with viscosupplement]
J3302	Injection, triamcinolone diacetate, per 5 mg [not covered if used with viscosupplement]
J3303	Injection, triamcinolone hexacetonide, per 5 mg [not covered if used with viscosupplement]
Other HCPCS codes related to the CPB:	
J1130	Injection, diclofenac sodium, 0.5 mg

Code	Code Description
ICD-10 codes covered if selection criteria are met:	
M17.0 - M17.32	Osteoarthritis of knee [not covered for viscosupplementation injection for patellofemoral arthritis]
M17.4 - M17.5	Other bilateral or unilateral secondary osteoarthritis of knee [not covered for viscosupplementation injection for patellofemoral arthritis]
M17.9	Osteoarthritis of knee, unspecified [not covered for viscosupplementation injection for patellofemoral arthritis]
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
G57.60 - G57.63	Lesion of plantar nerve [entrapment syndrome]
G81.10- G81.14	Spastic hemiplegia [hemiparesis]
L40.50 - L40.59	Arthropathic psoriasis
M12.30 - M12.39	Palindromic rheumatism
M15.0 - M16.9 M18.0 - M19.93	Osteoarthrosis and allied disorders [joints other than knee]
M20.20 – M20.22	Hallux rigidus
M22.40 - M22.42	Chondromalacia patellae
M24.551 - M24.559	Contracture, hip [femoro-acetabular impingement]
M25.561 - M25.569	Pain in knee
M26.601 - M26.69	Temporomandibular joint disorders
M36.2	Hemophilic arthropathy
M62.9	Disorder of muscle, unspecified [stiffness]
M79.2	Neuralgia and neuritis, unspecified [peripheral nerve pain]

Code	Code Description
M93.20 - M93.29	Osteochondritis dissecans

Background

U.S. Food and Drug Administration (FDA)-Approved Indications

- Treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen).

Viscosupplementation is a procedure in which hyaluronate is injected into the knee joint for treatment of osteoarthritis in the knee in persons who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen). 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/chondroiton 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.

Viscosupplementation is a therapeutic modality for the treatment of osteoarthritis based on the physiologic importance of hyaluronan in synovial joints (Bellamy, 2002). 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. Thus, the therapeutic goal of viscosupplementation 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. Controlled studies show that viscosupplementation with intra-articular injections of hyaluronate improve joint symptoms and may be effective in patients with mild-moderate degenerative joint disease of the knee.

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 hyaluoronate) 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.

In a prospective cohort study, Neustadt (2003) evaluated the long-term efficacy and safety of 5 weekly intra-articular (i.a.) injections of sodium hyaluronate (Hyalgan) in 76 patients (92 knees) with moderate to severe OA of the knee whose pain was not controlled by conventional measures. Thirteen patients had a repeat treatment course. A total of 72% of patients achieved greater than 50% improvement (defined by physical examination and assessment of pain using a visual analog scale [VAS]) for 1 year or longer; 9% of patients failed to achieve greater than 50% improvement for any period of time. The duration of response exceeded 2 years in some patients. Total knee replacement surgery was avoided or significantly delayed in 15 of 19 patients who were considering surgery prior to the injections. Ten of 15 (67%) knees improved after a repeat treatment course. Local adverse events were minor and infrequent. The author concluded that i.a. sodium hyaluronate was an effective and safe treatment for pain in difficult-to-treat patients with moderate to severe OA of the knee.

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.

In 2015, Bioventus launches Supartz FX which exapanded the safety label for repeat injection cycles in knee OA (Bioventus, 2015). Supartz FX is supplied as a sterile, non-pyrogenic solution in 2.5 mL pre-filled syringe administered once a week for a total of 5 injections. Each 2.5 mL contains 25 mg of sodium hyaluronate (hyaluronan).

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 syrinces. 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.

In a prospective, multi-center, open label, phase III clinical study, Benazzo et al (2016) evaluated the long-term efficacy and safety of Hymovis in the symptomatic treatment of knee osteoarthritis (OA). Two intra-articular injections (3 mL) of Hymovis (8 mg/mL HYADD 4) were administered 1 week apart at the beginning of the study on day 0 and day 7 and after 6 months from baseline, on day 182 and 189. Follow-up assessment were conducted for 52 weeks. The study included 50 subjects, 40 years old and older, with confirmed knee OA who had pain in the target knee. The variables considered were: WOMAC questionnaire, Joint Space Width (JSW), OMERACT OARSI responder criteria, EQ-5D questionnaire, rescue medication consumption. After the injections of Hymovis, pain perceived by the patient when walking on a flat surface (WOMAC A1 score) significantly improved at the end of the study respect to the baseline. WOMAC stiffness, physical function and total score significantly improved during the study since 3 months after treatment, and was maintained up to the end of the study ($p < 0.001$). By the x-ray analysis of knee, a radiological progression of OA was observed in the 26% of patients at the end of the study, while 88% of patients result to be responder to the therapy classified as per OMERACT-OARSI criteria. The EQ-5D weighted index increased significantly, against baseline, at each study time point ($p < 0.001$). Investigator's and patient's global assessment of the disease measured by the VAS both show a marked improvement in patient's health conditions. The authors concluded that

the results from this study confirm that Hymovis alleviates the knee pain since the first treatment cycle. The patients treated with two cycles of intra-articular injections of Hymovis had a progressive pain reduction that was maintained up to one year after the treatment start with improvement of all the scores considered in this study. Thus, Hymovis is effective and safe in symptomatic treatment of painful knee OA.

Sodium hyaluronate is available as Visco-3 (Bioventus LLC), which 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. Each one mL of Visco-3 contains 10 mg of sodium hyaluronate (hyaluronan) dissolved in a physiological saline (1.0% solution). The sodium hyaluronate (hyaluronan) is extracted from chicken combs. Sodium hyaluronate (hyaluronan) is a polysaccharide containing repeating disaccharide units of glucuronic acid and N-acetylglucosamine. Supplied as a sterile, non-pyogenic solution in 2.5 mL prefilled syringe (FDA, 2018). See Appendix for dosing information.

Sodium hyaluronate is available as TriVisc in a 3 mL prefilled syringe containing 2.5 mL of TriVisc. TriVisc is indicated for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, e.g., acetaminophen. TriVisc is administered by intra-articular injection as 3 doses, one week apart. TriVisc has the same chemical composition as GenVisc 850, except that GenVisc 850 is administered under a weekly 5-injection regimen of 2.5 ml per injection. Since TriVisc is of identical chemical formulation to GenVisc 850 (previously approved under P140005), all of the nonclinical studies used to provide evidence of the reasonable assurance of the safety of GenVisc 850 apply directly to TriVisc. The effectiveness of TriVisc was established from various nonclinical comparison studies of TriVisc and VISCO-3, which as the same indications for use as TriVisc and is also administered under a weekly 3-injection regimen of 2.5 ml per injection.

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 fluroscopic 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.

The use of an operating room and an anesthesiologist for intra-articular injections is not necessary.

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 hyaluronan 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 conclusion 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 can not 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 % confidence interval [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 % 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 Galacian 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 can not 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 can not 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 of13 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 6months

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 Duruoz 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 hyalurunate 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 +/- 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 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.

In a systematic review and meta-analysis, Leite and associates (2018) evaluated the efficacy of viscosupplementation (HA) on the pain and disability caused by hip OA, and determined the occurrence of AEs. Data sources included PubMed, Embase, Cochrane Library, ClinicalTrials.gov database, and specific journals up to March 2017; RCTs comparing HA with any other intra-articular injection were selected for analysis. Data were extracted according to Cochrane/Grades of Recommendation, Assessment, Development, and Evaluation criteria; 2 authors extracted data and assessed the risk of bias and quality of evidence. A random-effects meta-analysis was conducted. A total of 8 RCTs were retrieved (n = 807): 4 comparing HA to placebo; 3 to platelet-rich plasma (PRP); 3 to methylprednisolone; and 1 to mepivacaine; some RCTs had 3 arms. There was very low evidence that HA is not superior to placebo for pain at

3 months (standardized mean difference [SMD] = -0.06; 95 % CI: -0.38 to 0.25; p = 0.69), and high evidence that it is not superior in AEs (risk ratio [RR] = 1.21; 95 % CI: 0.79 to 1.86; p = 0.38). There is low evidence that HA is not superior to PRP for pain at 1 month. There is very low evidence that HA is not superior to PRP for pain at 6 and 12 months (MD in VAS [in cm]: -0.05 [95 % CI: -0.81 to 0.71], 1.0 [95 % CI: -1.5 to 3.50], and 0.81 [95 % CI: -1.11 to 2.73], respectively). There is high evidence that HA is no different from methylprednisolone for pain at 1 month (SMD = 0.02; 95 % CI: -0.18 to 0.22; p = 0.85). There is low evidence that HA is no different from methylprednisolone for Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International Responders Index at 1 month (RR = 0.44; 95 % CI: 0.10 to 1.95; p = 0.28). There is high evidence that HA is no different from methylprednisolone for AEs (RR = 1.21; 95 % CI: 0.79 to 1.87; p = 0.38). The authors concluded that they do not recommend viscosupplementation for hip OA. Compared with placebo, data showed scarce evidence of its efficacy up to 3 months, and suggested no difference at 6 months. However, they stated that future RCTs could present HA as an alternative to methylprednisolone for short-term symptom relief.

In a systematic review and meta-analysis, De Lucia and associates (2021) examined the long-term safety and effectiveness of single or 1 to 3 weekly injections of hylan G-F 20 at 1 year following the first injection for knee OA. Searches were conducted in PubMed/Medline, Embase, and CENTRAL and included relevant conference proceedings (January 1, 1995 to August 17, 2020); RCTs, non-randomized trials, and observational studies examining 1-year safety and effectiveness of 1 to 3 weekly injections or single hylan G-F 20 injection for knee OA were included. Primary outcomes were WOMAC pain, physical function, and stiffness. Meta-analyses of RCTs and non-randomized studies were conducted separately; and the search identified 24 eligible studies. Hylan G-F 20, in the meta-analyses of RCTs, showed statistically significant improvement in WOMAC pain (SMCC - 0.98, 95 % CI: - 1.50 to - 0.46), physical function (SMCC - 1.05, 95 % CI: - 1.28 to - 0.83), and stiffness (SMCC - 1.07, 95 % CI: -1.28 to -0.86). Improvement was also observed for VAS pain, SF-36 MCS (mental component summary), and SF-36 PCS (physical component summary). Analyses of non-randomized studies showed similar effectiveness estimates. There were no significant

differences in effectiveness based on injection schedule, nor between RCT and non-randomized studies. Rates of AEs were low for most types of AEs. Hylan G-F 20 (either as single or 1 to 3 weekly injections) showed improvement in 1-year effectiveness outcomes in comparison to baseline and was generally well-tolerated. The authors concluded that while further research will inform the medical field regarding viscosupplementation therapeutic options for knee OA, these findings showed that hylan G-F 20 at both frequencies/dosages were effective and generally well-tolerated for long-term use.

The authors stated that this meta-analysis had several drawbacks. First, as a consequence of the nature of OA treatment, most studies allowed additional concomitant medication or additional courses of hylan G-F 20. Studies that did not prohibit additional injections or concomitant treatments may have confounded the results. The potential confounding effects should be further studied, but such investigations were not feasible given the limitations of the data. Second, some of the meta-analyses had high levels of heterogeneity ($I^2 > 75\%$), potentially caused by variation in unmeasured patient characteristics. Third, attrition was high in the majority of these studies, which reduced the generalizability of these trials to all patients with knee OA who receive HA injections. Fourth, non-English studies were excluded, which could have introduced bias. Fifth, the focus of this meta-analysis was on a specific set of outcomes, and other outcomes could produce a different pattern of findings.

In a systematic review and meta-analysis, Wu and colleagues (2021) compared the safety and effectiveness of intra-articular HA injection with different molecular weights (MWs) for treating hip OA. These researchers carried out a systematic literature search for relevant studies in 3 electronic databases, including PubMed, BMJ Journals, and Cochrane Library, from inception to April 2020. Extracted outcomes included VAS (1, 3, and 6 months), Lequesne index (3 and 6 months), and adverse effects. HAs were classified into low-molecular-weight (LMW), moderate-molecular-weight (MMW), high-molecular-weight (HMW), and ultra-high-molecular-weight (UHMW) groups. Meta-analysis was carried out using Review Manager 5.3. A total of 15 studies with 614 patients were included. The meta-analysis showed that the HMW-HA group had the best improvement in VAS and Lequesne index compared with other HA

groups for all the follow-up visits. Moreover, the HMW group demonstrated significantly better improvement than the other groups in VAS at 6-month follow-up and in Lequesne index at 3- and 6-month follow-ups. Analysis for adverse effects revealed low rates of systemic adverse effects (less than or equal to 0.6 %) in all groups and similar rate of local adverse effects (around 10 %) among the groups except for UHMW-HA group (37.5 %). The authors concluded that among different MWs of HA in the treatment of hip OA, HMW-HA injection demonstrated the best effectiveness for up to 6 months following treatment without increased risk of adverse effects. Moreover, these researchers stated that further studies with more comprehensive data and a higher level of evidence are needed to prove these findings.

Amobarbital/Hyaluronic Acid Hydrogel for the Treatment of Post-Traumatic Osteoarthritis Prevention

Quarterman and colleagues (2022) noted that a mitochondrial electron transport chain member complex I inhibitor, amobarbital, can reduce oxidative damage and chondrocyte death, eventually preventing post-traumatic osteoarthritis (PTOA). Viscosupplementation using a cross-linked HA hydrogel is currently used clinically for knee OA pain relief. These researchers employed the HA hydrogel as a drug delivery vehicle to improve the long-term effectiveness of amobarbital. They examined the pharmaceutic stability of amobarbital when dispersed in a cross-linked HA hydrogel formulated in proportions intended for clinical use. These investigators validated a high-performance liquid chromatography with an ultraviolet detector (HPLC-UV) method following International Conference for Harmonization Q2(R1) guidelines to ensure its suitability for amobarbital detection. The feasibility of this formulation's drug delivery capability was proven by measuring the release, solubility, and drug uniformity. The amobarbital/HA hydrogel showed comparable amobarbital stability in different biological fluids compared to amobarbital solution. Furthermore, the amobarbital/HA hydrogel imparted significantly greater drug stability when stored at 70° C for 24 hours. The authors confirmed the pharmaceutical stability of the amobarbital/HA hydrogel in various conditions and biological fluids using a validated HPLC-UV method. These researchers stated that these results provided essential evidence in support of the use of this amobarbital/HA formulation in future clinical trials for the treatment of PTOA.

Ankle Osteoarthritis

Lee and colleagues (2022) noted that various non-operative treatments have been used to reduce pain and improve the QOL in patients with ankle OA. In a prospective clinical trial, these researchers examined the effectiveness and complications of hyaluronate injection using various clinical scoring systems. This study included 37 patients with unilateral ankle OA (grade 2 or 3 according to the Takakura classification) who did not respond to previous pharmacological treatment. A total of 3 weekly hyaluronate injections (2-ml Hyruan Plus) were administered. The effectiveness of intra-articular hyaluronate injection was examined on the basis of patient-reported foot and ankle clinical assessment at a mean follow-up of 13.8 ± 8.3 (range of 6 to 33) months. Ankle Osteoarthritis Scale scores for pain and disability, American Orthopedic Foot and Ankle Society (AOFAS) ankle-hindfoot scores, and VAS for pain significantly improved at the final follow-up compared to that before intra-articular hyaluronate injection ($p \leq 0.05$). When patients were dichotomized according to age, sex, BMI, symptom duration, and Takakura classification, all these factors were not related to clinical outcomes. The authors concluded that the findings of this study suggested that 3 weekly intra-articular hyaluronate injections could be carried out safely to reduce pain and improve function without serious complications in patients with early or intermediate-grade ankle OA when patients inadequately respond to medication. Moreover, these researchers stated that larger controlled studies are needed to clarify the effects of hyaluronate injection and identify patients who could benefit most from hyaluronate injection. Level of Evidence = III.

Combined Ozone Gas and Viscosupplementation for the Treatment of Knee Osteoarthritis

Giombini et al (2016) compared short-term clinical outcomes between IA injection of HA, oxygen ozone (O2O3), and the combination of both, in patients affected by OA of the knee. A total of 70 patients (age of 45 to 75 years) with knee OA were randomized to IA injections of HA (n = 23), or O2O3 (n = 23) or combined (n = 24) 1 per week for 5 consecutive weeks. KOOS questionnaire and VAS, before treatment (pre) at the end (post), and at 2 months after treatment ended (follow-up) were used as outcome measures. Analysis showed a significant effect ($p < 0.05$) of the

conditions (pre, post and follow-up) in all parameters of the KOOS score and a significant effect ($p < 0.05$) of groups (HA, O2O3 and combined) for pain, symptoms, activities of daily living (ADL) and QOL. The combined group scores were higher compared to the HA and O2O3 groups, especially at follow-up. The authors concluded that the combination of O2O3 and HA treatment led to a significantly better outcome especially at 2-month follow-up compared to HA and O2O3 given separately to patients affected by OA of the knee. This was a relatively small study (n = 24 in the combination group) with a short-term follow-up (2 months). These preliminary findings need to be validated by well-designed studies.

Duymus et al (2017) compared the effectiveness of treatment in 3 groups of patients with knee OA given an IA injection of PRP, HA or ozone gas. A total of 102 patients with mild-moderate and moderate knee OA who presented at the polyclinic with at least a 1-year history of knee pain and VAS score of greater than or equal to 4 were randomly assigned to 3 groups. Group 1 (PRP group) received IA injection of PRP × 2 doses, Group 2 (HA group) received a single dose of HA, and Group 3 (Ozone group) received ozone × 4 doses. Weight-bearing anteroposterior-lateral and Merchant's radiographs of both knees were evaluated. WOMAC and VAS scores were applied to all patients on first presentation and at 1, 3, 6 and 12 months. At the end of the 1st month after injection, significant improvements were observed in all groups. In the 3rd month, the improvements in WOMAC and VAS scores were similar in Groups 1 and 2, while those in Group 3 were lower ($p < 0.001$). At the 6th month, while the clinical effectiveness of PRP and HA were similar and continued, the clinical effect of ozone had disappeared ($p < 0.001$). At the end of the 12th month, PRP was determined to be both statistically and clinically superior to HA ($p < 0.001$). The authors concluded that in the treatment of mild-moderate knee OA, PRP was more successful than HA and ozone injections, as the application alone was sufficient to provide at least 12 months of pain-free ADLs. This study did not address the use of combined ozone and HA injection. Moreover, ozone therapy appeared the least effective among the 3 therapies for knee OA.

Silva et al (2020) examined reticulated HA alone or associated with ozone gas in the treatment of OA due to hip dysplasia in dogs. A total of 14 client-owned dogs were randomly assigned into 2 groups: Group 1 --

single IA injection of HA; Group 2 -- single IA infiltration injection of HA associated with ozone gas. Each hip joint received an average of 0.75-ml of reticulated HA US-guided. Ozone gas at a dose of 45 µg/ml was incorporated into HA by insufflation. Dogs were evaluated for body condition scoring, orthopedic examination and radiographic scores of the hip joints, goniometric measurements of the hip joints, visual gait score, and kinetic analysis. The evaluations were conducted immediately before treatments (M0), and at days 30 (M1), 60 (M2), and 90 (M3) after treatments. There were no significant differences in body mass and body condition scoring (5-point scale) in each group in all evaluation moments. The scores of orthopedic examination of the hip joints showed statistical differences in each group between moments (M0 > M3), but differences were not observed between groups. No statistical differences were found for radiographic scores in each group between moments, but differences were observed between groups immediately prior to treatments (G1 > G2) and 90 (G1 > G2) after treatments. Goniometric measurements of hip flexion and extension showed no significant differences in each group between moments or between groups. No statistical differences between groups were found concerning the lameness score. There were significant differences for lameness score among moments in Group 1, being M0 > M2 and M0 > M3, and Group 2 in which M0 > M1, M0 > M2, and M0 > M3. The mean percentage of change of peak vertical force (PVF) and vertical impulse (VI) between M3 and M0 in Group 1 was almost null and in Group 2 was positive, being 31.1 ± 29.4 and 10.6 ± 25.4, respectively. The authors concluded that IA viscosupplementation alone or associated with ozone gas allowed improvement of lameness scores and orthopedic examination score. In Group 2 the association of ozone gas had better results on kinetic analysis.

These researchers stated that despite randomization, radiographic scores were higher in G1 than G2. On the other hand, the radiographic findings did not influence the scores of orthopedic examination or lameness score; thus, the absence of difference between 2 groups for other parameters had suggested that a single application of ozone was unable to avoid radiographic progression of OA and improvement in hip extension and flexion. In a comparative study in human patients with knee OA, the group that received IA injection of HA in combination with oxygen ozone showed better outcome than HA or ozone administered separately, however, the applications were once-weekly for 5 consecutive weeks.

These investigators stated that further studies are needed to clarify, including an ozone group, which may consider one of the limitations of the present study. Because IA route in dogs generally requires sedation and/or anesthesia, another option would be rectal insufflation, as used in human patients with rheumatoid arthritis. Another drawback of this study was the use of heterogeneous groups of dogs, which made difficult the kinetic evaluation. Furthermore, the dogs were evaluated walking, because of the disease the dog may be unable to trot or have difficult to gait trial repetition, despite trotting gait be considered more sensitive than walking gait to lameness detection. Therefore, to avoid these influences future studies using dogs of the same breed and with the same hip scoring should be considered.

Furthermore, an UpToDate review on “Overview of the management of osteoarthritis” (Deveza, 2020) does not mention ozone as a management / therapeutic option.

Combined Use of Viscosupplementation and Other Intra-Articular Injectates

In a randomized double-blind study, Palmieri et al (2013) examined the effect of a highly cross-linked hyaluronic acid (HA), Variofill, alone or in combination with diclofenac sodium or sodium clodronate, for management of bilateral knee osteoarthritis-related pain. A total of 62 patients with symptomatic bilateral medial tibiofemoral knee osteoarthritis (Kellgren-Lawrence grade II and III) and pain in both knees corresponding to a daily visual analog scale (VAS) score greater than or equal to 30 in the month before the beginning of the study were included in this investigation. Patients were divided into 3 groups: group 1, treated with an injection of HA alone (66 mg) into each knee; group 2, treated with an injection of HA (49.5 mg) plus diclofenac sodium (5 mg) into each knee; group 3, treated with an injection of HA (49.5 mg) plus sodium clodronate (5 mg) into each knee. Patients also underwent blood tests for measurement of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) immediately before and at 6-month follow-up. Hyaluronic acid alone and in combination with sodium clodronate or diclofenac sodium produced a significant improvement in mean VAS pain score at 3 and 6-month follow-up. At 6-month follow-up, therapy with HA plus sodium clodronate was the most beneficial in terms of percentage

improvement in VAS pain score. A significant improvement in ESR and CRP was observed at 6-month follow-up in each treatment group. No significant difference was observed when the percentage change from baseline related to these parameters was compared among the groups. No drop-out was observed in any group. No serious adverse events were observed. The authors concluded that further studies are needed to determine the effect of a therapy based on HA combined with diclofenac sodium or sodium clodronate in larger cohorts of patients affected by knee osteoarthritis and in longer-term follow-up.

In a randomized clinical trial, de Campos et al (2013) addressed 3 questions: Does the addition of triamcinolone to viscosupplementation (i) improve 1st-week pain and function compared with viscosupplementation alone, (ii) diminish adverse effects of viscosupplementation alone, and (iii) alter 6-month pain and function of viscosupplementation alone? These researchers prospectively enrolled 104 patients with knee osteoarthritis and randomized them to receive either a single intra-articular injection (6 ml) of hylan GF-20 (Group viscosupplementation [Group VS]), or a single intra-articular injection of hylan GF-20 (6 ml) and 1 ml (20 mg) of triamcinolone hexacetonide (Group VS + T). VAS, WOMAC, and Lequesne questionnaires were completed at baseline and at weeks 1, 4, 12, and 24. At week 1 the WOMAC and VAS scores were lower in Group VS + T, compared with Group VS. There was no difference regarding the adverse effects. At weeks 4, 12, and 24 there were no differences in the groups. The authors concluded that the addition of triamcinolone hexacetonide improved 1st-week symptom and functional scores of viscosupplementation, but not beyond. It did not appear to increase the likelihood of adverse effects. They also stated that one can speculate that triamcinolone could positively affect the action in disease progression; however, more studies are needed on this matter.

Migliore et al (2014) evaluated the mid-term pain-relief effect of an ultrasound-guided injection of HA combined with a high concentration of sorbitol (SynolisV-A (ANTI-OX-VS)) in patients suffering from symptomatic hip osteoarthritis. Lequesne index, Health Assessment Questionnaire (HAQ), pain reduction, Global Patient Assessment (GPA), Global Medical Assessment (GMA) and reduction in monthly analgesic

consumption were assessed during the 12-month follow-up after the injection. A total of 20 patients were enrolled in the study and received 1 IA US-guided injection of 2 syringes of ANTI-OX-VS into the target hip; 11 drop-out patients were registered, of whom 2 were for loss of efficacy at 6 months, 1 for loss of efficacy at 9 months and 8 patients for severe co-morbidities. Mean scores of all clinical parameters evaluated at each control visit were significantly different when compared with baseline mean value. No systemic adverse events were observed. Even though the sample size of this study was limited, the results suggested a durable good efficacy of a 4-ml single injection of ANTI-OX-VS in hip OA, at least for the patients who completed the study. The authors concluded that a larger number of patients and an RCT are needed to confirm these data, investigating also the predictive factors of clinical response to ANTI-OX-VS.

In a pilot study, Conrozier et al (2016) provided data from daily practice conditions of a viscosupplement made of a cross-linked high-molecular-weight HA combined with mannitol in patients with knee osteoarthritis (KOA). The data of 40 consecutive patients, 29 women and 11 men, who were prospectively followed-up for 6 months, using a standardized procedure, were retrospectively analyzed. All patients have received a single intra-articular injection of HAnox-M-XL (4.4 ml), viscosupplement made of a cross-linked HA (16 mg/ml) + mannitol (35 mg/ml), in the target knee. The primary outcome was safety. The secondary end-points included 3- and 6-month change in the WOMAC pain (0 to 50) and WOMAC total (0 to 240) and patient's global assessment (PGA). Patient's self-assessment of treatment efficacy (0 to 3) and analgesic consumption were obtained at months 3 and 6. An intent-to-treat analysis was performed. Mean (SD) age was 60.7 (13.9) years, and mean body mass index (BMI) was 28.6 (5.0). Kellgren-Lawrence radiological grade was I/II and III/IV in 13 and 27 of the subjects, respectively. The average WOMAC pain and WOMAC total scores at baseline were 21.5 (9.8) and 89.9 (42.8), respectively; 39 patients completed the follow-up. HAnox-M-XL was well-tolerated; 2 patients experienced knee pain after injection, which resolved within 3 days. No treatment-related severe adverse event was reported. Mean (SD) variations in WOMAC pain and WOMAC total scores were -8.2 (8.9) and -38.4 (35.6), respectively, at month 6 ($p = 0.001$); PGA decreased from 5.5 (2.0) to 3.0 (2.2) ($p = 0.006$). Efficacy was rated as good or very good in 76.9 % of the cases. Most of the

regular analgesics users decreased their consumption. The authors concluded that treatment with 1 injection of 4.4-ml HAnox-M-XL was effective to alleviate KOA symptoms over 6 months, without safety concern. Moreover, they stated that controlled trials are needed to confirm these pilot data.

Russo et al (2016) evaluated the rheological and biological properties of different HA compositions in combination with platelet-rich plasma (PRP) in order to identify (i) the viscoelastic features of the HA-PRP blends, (ii) their biological effect on osteoarthritic chondrocytes, and (iii) HA formulations suitable for use in combination with PRP. HA/PRP blends have been obtained mixing human PRP and 3 different HA at different concentrations: (i) Sinovial, 0.8 % (SN); (ii) Sinovial Forte 1.6 % (SF); (iii) Sinovial HL 3.2 % (HL); and (iv) Hyalubrix 1.5 % (HX). Combinations of phosphate buffered saline (PBS) and the 4 HA types were used as control. Rheological measurements were performed on an Anton PaarMCR-302 rheometer. Amplitude sweep, frequency sweep and rotational measurements were performed and viscoelastic properties were evaluated. The rheological data were validated performing the tests in presence of Bovine Serum Albumin (BSA) up to ultra-physiological concentration (7 %). Primary osteoarthritic chondrocytes were cultured in-vitro with the HA and PRP blends in the culture medium for 1 week. Cell viability, proliferation and glycosaminoglycan (GAG) content were assessed. PRP addition to HA led to a decrease of viscoelastic shear moduli and increase of the cross-over point, due to a pure dilution effect. For viscosupplements with HA concentration below 1 % the viscoelasticity is mostly lost. Results were validated also in presence of proteins, which in synovial fluid were more abundant than HA. Chondrocytes proliferated overtime in all different culture conditions. The proliferation rate was higher in chondrocytes cultured in the media containing PRP compared to the cultures with different HA alone. GAG content was significantly higher in chondrocytes cultured in PRP and HL blend. The authors investigated the rheological and biological properties of 4 different HA concentrations when combined with PRP giving insights on viscoelastic and biological properties of a promising approach for future OA therapy. The authors stated that these findings demonstrated that PRP addition was not detrimental to the viscosupplementation effect of HA. They noted that

viscosupplements containing low HA concentration are not indicated for combination with PRP, as the viscoelastic properties are lost.

Vannabouathong et al. (2018) state that intra-articular injections are commonly used to treat arthritis of the knee; however, the efficacy for arthritis of the ankle is debatable. The authors conducted a systematic literature review of observational and randomized clinical trials that include treatments with corticosteroids (CS), hyaluronic acid (HA, platelet-rich plasma (PRP) and mesenchymal stem cells (MSC). The authors found 27 studies on 1085 patients that included mainly observational studies (n=20). The only RCTs were those evaluating HA. Case series demonstrated favorable results in terms of symptomatic relief with CS, HA, PRP, and MSC injections; however, the effects of CS may only be short term and the evidence on MSCs was limited to 1 study with 6 ankle OA patients. Pooled results (3 RCTs, 109 patients) suggested significantly improved Ankle Osteoarthritis Scale scores with HA over saline at 6 months, with a mean difference of 12.47 points (p= .03). The authors concluded that the evidence from small trials favors HA and PRP injections for the treatment of pain associated with ankle osteoarthritis; however, the relative efficacy of all injectable therapies is far from definitive and warrants further high-quality comparative trials.

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 IAKIs 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 IAKIs 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 IAKIs 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 IAKIs 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 IAKIs. The authors concluded that image-guided IAKIs are modestly more accurate than blinded IAKIs 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.

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 he 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.

Following Arthroscopic Knee Surgery / Partial Meniscectomy

Tripathy et al (2022) stated that pain, swelling and joint stiffness are the major problems following arthroscopic ACLR surgery that restrict early return to sports and athletic activities. The patients often receive prolonged analgesic medications to control the inflammatory response and resume the pre-injury activities. In a systematic review, these researchers examined the safety and effectiveness of IA HA injection following ACLR. They carried out a literature search of electronic databases and a manual search of studies reporting clinical effectiveness of IA HA following ACLR on November 1, 2020. The quality of the methodology and risk of bias was assessed using the Cochrane

Collaboration Risk of Bias Tool and Newcastle-Ottawa scale for RCT and prospective cohort studies, respectively. Of 324 studies retrieved, 4 studies (3 RCTs and 1 prospective cohort study) were found to be suitable for inclusion in this review. These studies had a low-to-moderate risk of bias. There were 182 patients in the HA group and 121 patients in the control group. The demographic characteristics of the patients were similar in all studies. The pooled analysis of studies examining pain at different follow-up periods (2-week, 4-6 weeks, 8-12 weeks) after ACLR revealed no significant difference between the HA and control groups ($p > 0.05$). The knee swelling was significantly less in the HA group at 2 weeks (MD -7.85, 95 % CI: -15.03 to -0.68, $p = 0.03$, $I2 = 0$ %), but no such difference was noted after 4-6 weeks and 8-12 weeks. The functional outcome score was not significantly different between the groups (SMD 0.00, 95 % CI: 0.38 to 0.38, $p = 0.99$, $I2 = 0$ %). The authors concluded that although the individual study demonstrated a short-term positive response regarding pain control and swelling reduction, the pooled analysis did not find any clinical benefit of IA HA injection following ACLR surgery. Level of Evidence = II.

In a RCT, Yoon et al (2022) examined the effectiveness of viscosupplementation after arthroscopic partial meniscectomy. This trial included 47 patients who underwent arthroscopic partial meniscectomy between March 2020 and March 2021. Patients were randomized into 2 groups: a viscosupplementation group (n = 23) and a control group (n = 24). A single-dose IA HA injection was used as viscosupplementation. The 100-mm VAS for pain assessment was measured at baseline and at 1 day, 2 weeks, 6 weeks, and 3 months post-surgery. The IKDC, Tegner, Lysholm, and WOMAC scores and ROM of the knee were measured at baseline, 2 weeks, 6 weeks, and 3 months. The 100-mm VAS score for pain was significantly lower in the viscosupplementation group at 2 weeks post-surgery (27.5 mm versus 40.7 mm, $p = 0.047$). ROM was significantly greater in the viscosupplementation group than in the control group at 2 weeks (131.5° versus 121.0°, $p = 0.044$) post-surgery. No significant differences were observed in the IKDC or in the Tegner, Lysholm, and WOMAC scores between the 2 groups. The authors concluded that this prospective, randomized clinical trial showed that viscosupplementation after arthroscopic partial meniscectomy significantly reduced pain at 2 weeks post-surgery and improved ROM at 2 weeks post-surgery. Thus, viscosupplementation may provide some

benefits in terms of pain and functional recovery after arthroscopic surgery. Moreover, these researchers stated that further investigation with a larger number of samples is needed for a more definitive conclusion. Level of Evidence = I.

The authors stated that this study had several drawbacks. First, the surgeon was not blinded to the study. Second, even though bias was eliminated, the amount of resected meniscus was difficult to quantify. As the extent of meniscal resection is related to worsened clinical outcomes, this factor may have affected the results of this clinical trial. Third, this study included a small sample (n = 23 in the viscosupplementation group). Third, medial meniscectomy tends to result in better outcomes than lateral meniscectomy. These researchers stated that future studies focusing on medial or lateral meniscectomy should be performed.

Mao et al (2023) noted that HA intra-articular injection after arthroscopic knee surgery has been widely employed; however, its safety and effectiveness remain controversial. In a systematic review, these investigators examined analyze the safety and effectiveness of HA intra-articular injection after arthroscopic knee surgery; and compared the effectiveness of HA with different molecular weights. They carried out a literature search in PubMed, Embase, Google scholar and the Cochrane library from inception to September 16, 2022 for English-written articles to identify RCTs that evaluated the clinical safety and/or effectiveness of HA intra-articular injection after arthroscopic knee surgery. These researchers meta-analyzed the outcomes of patients given intra-articular HA injections post-operatively and control patients. They also examined the influence of HA with different molecular weights. In every calculation, sensitive analysis was conducted. The VAS for pain, WOMAC and AEs were selected as the primary outcome measurements, while Lysholm, IKDC and Tegner score were selected as the secondary outcome measurements. Publication bias of every outcome was evaluated using egger test. A total of 15 studies involving 951 knees were included and 12 of them were used to carry out the meta-analysis. The results showed no significant difference between the HA group and control group according to VAS, whether assessed at less ($p = 0.90$) or more than 6 months ($p = 0.55$). Furthermore, there were no statistical differences between the HA group and control group according to subgroup analysis ($p = 0.77$, 0.91 and 0.81 in anterior cruciate ligament reconstruction

[ACLR], meniscectomy and overall groups, respectively). Compared to control group, the overall effect of WOMAC score showed no significant differences (p = 0.25), nor did in 2 subgroups (p = 0.37 and P = 0.22). Outcomes measured by Lysholm (p = 0.13), IKDC (p = 0.86) and Tegner (p = 0.42) scores showed no significant differences, either. The analysis of the risk of AEs indicated no increase in HA groups (p = 0.06). These investigators found no significant differences between high- and low-molecular-weight HA at 6 (p = 0.96) or 12 months (p = 0.93) post-operatively. Two studies failed to pass the sensitive analysis and the reasons were discussed detailly and acceptable publication bias was observed. The authors concluded that although HA injection after arthroscopic knee surgery was safe, the available evidence did not support its effectiveness in pain relief and functional recovery. Thus, the use of HA injection after arthroscopic knee surgery is not recommended.

Following Meniscectomy

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.

Intra-Articular Hyaluronic Acid Injection for the Treatment of Hip Osteoarthritis

Letizia Mauro et al (2017) stated that OA is the most common joint disorder in the elderly, causing significant pain which negatively affects mobility and quality of life (QOL). In a prospective, open-label, single-site, investigator-initiated study, these researchers evaluated the effectiveness of US-guided intra-articular injections of Hyalubrix combined with exercise therapy in the treatment of hip OA. A total of 40 patients were enrolled and received 3 US-guided injections of Hyalubrix, 45 days apart, combined with 3 sessions a week of physical therapy (proprioceptive rehabilitation of the lower limbs; gait training; balance training) up to a total of 30 sessions (10 weeks), starting from 1 week after the 1st injection. The primary objective was to achieve a lasting reduction in OA symptoms related to pain during activity. During the course of the study the pain perceived by the patient during activity dropped from a mean value of 6.94 cm to a mean value of 1.46 cm and showed a statistically significant decrease from visit 1 compared to baseline ($p < 0.05$), which was confirmed at all the subsequent time-points. Significant improvements were also observed in the evaluation of the secondary objectives: hip disability; OA-related pain at rest; daily functioning and NSAIDs intake. The authors concluded that findings of this study demonstrated a significant improvement in OA-related pain, hip disability, and patient's daily functioning as well as a reduction in NSAIDs intake. Patients suffering from hip OA appeared to benefit from the treatment with Hyalubrix injections plus exercise therapy. Moreover, these investigators stated that a further controlled study is needed to evaluate the synergic effect of the 2 combined treatments. The main drawbacks of this study were its small sample size (n = 40) and the lack of a control group; and the findings were confounded by the combined use of HA injections and exercise therapy.

Clementi et al (2018) stated that viscosupplementation with HA is increasingly used for the treatment of hip OA. These researchers compared the efficacy of intra-articular injections of an ultra-high molecular weight viscosupplement (UHMW-HA, Fermathron S) with a medium molecular weight hyaluronan (MMW-HA, Hyalubrix 60) in hip OA. A total of 54 patients with hip OA grade-3 on the Kellgren/Lawrence scale were randomized. All infiltrations were performed under US

guidance. Evaluation was performed pre-operatively and at 1, 3, 6 and 12 months after infiltration. Patients were clinically evaluated using Lequesne index, VAS and WOMAC score. A total of 50 patients, including 27 in the MMW-HA group and 23 in the UHMW-HA group, completed the follow-up. No significant difference was found between the 2 groups in terms of VAS, WOMAC or Lequesne index pre-operatively or at 1, 3, 6 and 12 months after viscosupplementation. A stratified analysis was performed to study the development over time of Lequesne index of patients aged less than or equal to 55 years, greater than 55 and, less than or equal to 70 years and greater than 70 years and Lequesne index was different between the 3 age-stratified subgroups only in the MMW-HA group. The subgroup of older patients showed a higher Lequesne index than the subgroups of younger patients ($p < 0.05$). The authors concluded that UHMW-HA was a safe and effective treatment for hip OA; a single dose of UHMW-HA was as effective as 2 doses of MMW-HA resulting in similar reductions of pain and disability. Moreover, these researchers stated that future studies with a larger sample size are needed to confirm the long-term efficacy of a single infiltration of the UHMW-HA formulation.

The authors stated that this study had several drawbacks. First, these investigators evaluated patients only with the Kellgren-Lawrence (KL) scale for radiological assessment, while MRI would be better suited to evaluate the degree and extent of the cartilage degeneration. In fact, a new MRI hip OA grading system (SHOMRI) has recently been developed, that is practical in image acquisition and scoring; this new grading system showed good intra- and inter-reader reproducibility and found a significant correlation with radiographic and clinical scores, which are the current standards of reference for hip OA such as KL scale. Another drawback was the lack of a placebo group. Placebo injections may cause an important reduction in pain relief, especially during the 1st week. Moreover the effect of the injections was only evaluated using subjective clinical scores and no objective evaluation or imaging of the progress. Sample size was too small to draw accurate conclusions from the comparison between the 2 treatments ($n = 27$ and $n = 23$, respectively). Furthermore, the follow-up period of 1 year did not allow an assessment to be made of whether treatment with UHMW-HA determined a delay in the need for total hip arthroplasty (THA).

Letizia Mauro et al (2018) noted that although viscosupplementation has been used in the past few years both for knee and hip OA, the number of intra-articular injections and the interval between doses still remains an undetermined subject. In an open-label, retrospective study , these researchers examined the clinical and functional outcome in patients with mild-moderate hip OA treated with a course of 1, 2 or 3 HA intra-articular injections. A total of 96 patients were included: 19 patients received only 1 injection, 24 received 2 injections, and 44 received 3 injections. Age, sex, VAS for pain and WOMAC score before each intra-articular injection, number of intra-articular injections, reasons for interrupting the treatment, AEs, time between HA injections, and number of patients who had a THA were retrieved from the medical records of each patient. VAS and WOMAC scores were obtained from all patients also at a mean follow-up of 7 months after the last hip injection. All patients who received 1, 2 or 3 hip injections improved in VAS and WOMAC score; 3 intra-articular injections provided a better outcome in terms of pain reduction compared to 1 or 2 injections. The authors concluded that intra-articular HA injections for mild-moderate hip OA were demonstrated to be effective in reducing pain and improving function; a full course of 3 injections provided the best result in pain control. The authors stated that limitations of this study included the lack of a control group, and other possible therapies used by the subjects during HA treatment that could have influenced the outcomes, were not registered.

Brander et al (2019) noted that hip OA is difficult to treat. Steroid injections reduce pain with short duration. With widespread adoption of office-based, image-guided injections, HA is a potentially relevant therapy. In a randomized, double-blind, multi-center, saline placebo-controlled trial, these researchers compared the safety and effectiveness of a single 6-ml image-guided injection of hylan G-F 20 to saline in painful hip OA. A total of 357 patients were enrolled. Subjects were greater than or equal to 35 years of age, with painful (WOMAC-A1: 5.0 to 8.0; numeric rating scale [NRS]: 0 to 10) mild-to-moderate hip OA (KL grade II/III) and minimal contralateral hip pain (WOMAC-A1 less than 4). Outcome measures included "pain on walking" (WOMAC-A1 and -A), Patient Global Self-Assessment (PTGA), WOMAC-A1 responder rate (+ greater than or equal to 2 points on NRS), and AEs over 26 weeks. A total of 357 patients (hylan G-F 20 single: n = 182; saline: n = 175) were enrolled. Both groups demonstrated significant pain improvement from baseline

over 26 weeks ($p < 0.0001$); saline-induced pain reduction was a remarkable 35 %. WOMAC-A and PTGA scores also significantly improved ($p < 0.0001$). No statistically significant difference was observed between groups in WOMAC-A1 scores (hylan G-F 20 single:-2.19 ± 0.16; saline:-2.26 ± 0.17) or WOMAC-A1 responders (41 to 52 %). Treatment-related AE rates at target hip were similar (hylan G-F 20 single:23 patients [12.8 %]; saline:12 [7.0 %]). Post-hoc analysis found, despite protocol requirements, many patients had psychological (31 %) or potential neuropathic pain (27.5 %) conditions. The authors concluded that a single 6-ml hylan G-F 20 injection or saline for painful hip OA resulted in similar, statistically significant/clinically relevant pain and function improvements up to 6 months following injection; no differences between hylan G-F 20 and saline placebo were observed.

Furthermore, an UpToDate review on "Overview of the management of osteoarthritis" (Deveza, 2020) states that "In addition to benefits, side effect profile, and patient-specific impairments and preferences, costs of interventions and local availability should also be considered. As an example, intraarticular hyaluronic acid injections are associated with high costs without clinically significant benefits over intraarticular placebo … The benefit of intraarticular hyaluronic acid (HA) is also controversial for knee and hip OA, and most evidence demonstrates only a small superiority over intraarticular placebo".

Intra-Articular Injection of an Hexadecylamide Derivative of Hyaluronic Acid for the Treatment of Femoro-Acetabular Impingement

Ometti and colleagues (2020) stated that femoro-acetabular impingement (FAI) is a condition that has been increasingly recognized as a source of hip pain and a possible risk factor to early development of hip OA. To the authors' knowledge, the use of HA in the treatment of FAI has been examined only by 2 studies, both using a high molecular weight HA. These researchers examined the effectiveness of 2 weekly injections of an hexadecylamide derivative of HA (HYADD4-G, Hymovis) for the treatment of FAI. All patients received 2 weekly intra-articular injections of Hymovis at baseline and after 7 days. Clinical and functional assessments were carried out at baseline and was repeated after 1, 3, 6 and 12 months. Functional measures included VAS for pain, Harris Hip

score (HHS), Lequesne Index (LI), Tegner activity level scale (TALS) and monthly consumption of NSAIDs. A total of 21 hips (19 patients, 2 bilateral cases) were treated. The variables VAS, HHS as well as Lequesne improved significantly from T0 to T4 (at 12 months) with the best improvement between T0 and T1. At the same time, a reduction in NSAIDs monthly intake was registered. On the other hand, a significant improvement in Tegner scale was not observed; no AEs were registered. The authors concluded that 1 cycle of HYADD4-G could be a safe and effective treatment in patients with FAI, showing significative results in term of pain control as well as hip functionality and QOL up to 1 year. However, these investigators stated that although this study showed positive results, several drawbacks must be addressed. A larger sample size would be preferred to avoid selection bias. Moreover, due to the lack of a placebo arm, a potential placebo effect could not be ruled out. However, since the effectiveness of an hexadecylamide derivate of HA in FAI has never been examined, the objective of this trial was primarily to examine its effects on FAI as well as to give a starting point for further research.

Platelet-Rich Plasma Combined with Hyaluronic Acid for the Treatment of Knee Osteoarthritis

Palco and colleagues (2021) noted that knee OA is one of the most common joint diseases resulting in knee pain and reduction of mobility, with a negative effect on QOL; IA injections of different formulations of PRP are an increasingly common non-surgical treatment for knee OA. Recently, in order to combine the anti-inflammatory effect of PRP and the viscosupplementation effect of HA, a formulation of PRP combined with hyaluronic acid (PRP + HA) has been proposed. In a retrospective study, these researchers compared the effectiveness of plasma with high concentration of platelets and leukocytes (L-PRP) with PRP + HA in patients with mild-to-moderate (Kellgren-Lawrence scale II to III grade) knee OA. Among the 51 patients included, 28 have been treated with L-PRP, while 23 with PRP + HA. Evaluation at baseline (T0), after 3 months (T1) and 1 year (T2) were carried out. The outcome analyzed were the Knee Society Score (KSS), VAS (at T0, T1, and T2) and the KOOS (T0 and T2). These investigators examined change in mean scores within and between groups among different time-points using repeated measures ANCOVA. Although both treatments have been

effective in reducing VAS, the group treated with PRP + HA showed a significantly lower KSS. The authors concluded that these findings showed that the use of both treatments may aid in reducing pain in patients with mild-to-moderate knee OA. Moreover, PRP + HA showed better results in improving knee mobility and function. These researchers stated that the findings of this study should be considered only preliminary; further investigations (e.g., comparative studies with other non-surgical options or studies that examine their effectiveness in severe OA or in other degenerative joint diseases) are needed to determine the clinical effectiveness of these formulations.

The authors stated that this study had several drawbacks. First, due to the retrospective nature of the study, the baseline scores in examination were derived from a single measurement on a non-random sample. Hence, in this study, both design and analysis did not account for the regression to the means; thus, the results should only be considered preliminary. Second, these researchers treated patients who did not respond to analgesic/anti-inflammatory therapy, and they interviewed patients regarding their drugs consumption (to exclude routine analgesic/anti-inflammatory drugs users). Nevertheless, these investigators did not systematically collect concomitant treatment; thus, they could not report the occasional consumption of analgesic/anti-inflammatory drugs from the patients. Third, the absence of follow-up after 1-year. At this time-point, the benefits of treatment were still observable; however, these researchers were unable to determine how much they persisted, or if the outcomes lasted longer in one group or in the other. Fourth, due to the retrospective nature of the study, these investigators did not have the possibility to compare the effects with placebo, with saline, or especially with other combinations (e.g., PRP only, or L-PRP + HA). Fifth, despite partly accounting for the possible selection bias by adjusting for age, a proper analysis based on matching, if feasible (e.g., prospective setting) may have been superior.

Shoulder Osteoarthritis

Kany and colleagues (2021) stated that OA of the shoulder in individuals less than 50 years of age is rare; and treatment is delicate. Shoulder replacement incurs frequent long-term risk of progression and a high revision rate, making it unsuitable to young active patients. In a

retrospective, multi-center study, these researchers determined the epidemiology of shoulder OA in under 50-year-old subjects and examined the clinical results of the various therapeutic options. These researchers hypothesized that well-conducted, non-operative treatment could allow shoulder replacement to be postponed. The secondary hypothesis was that anatomic total shoulder arthroplasty (TSA) is the treatment of choice when other options fail. This trial included primary OA (POA) and post-instability OA (PIOA) in patients aged less than or equal to 50years at symptom onset. Exclusion criteria comprised post-traumatic OA, rheumatoid arthritis (RA) and necrosis. A total of 266 patients (273 shoulders) were included from 13 shoulder surgery centers: 2 types of non-operative treatment (28 by PRP and 88 by viscosupplementation), 73 arthroscopies, and 150 implantations (62 humeral hemi-arthroplasties [HA], comprising 10 hemi-metal, 24 hemi-pyrocarbon and 28 hemi-resurfacing; 77 anatomic total prostheses, and 11 reverse prostheses). Minimum follow-up was 12 months for non-operative treatment and 24 months for arthroplasty (some patients having both). Endpoints comprised Constant score, Subjective Shoulder Value (SSV) and number of complications/revision procedures. Mean age at treatment was 43 years (range of 23 to 65 years), with 75 % male predominance. Symptom onset was earlier in PIOA than in POA: 36 versus 39 years (range of 20 to 50 years). PRP and viscosupplementation postponed implantation by a mean 3.5 years in 86 % of cases, as did arthroscopy in 56 %; external rotation with elbow to side (ER1) restriction was the most negative factor. At 74 months' follow-up for HA and 95 months for TSA, mean Constant score was significantly lower for HA (56 versus 67; p = 0.004), with higher rates of complications (31 % versus 11 %) and implant exchange (13 % versus 9 %). The authors concluded that PRP, viscosupplementation and arthroscopy allow implantation to be postponed until the shoulder becomes stiff and painful. In case of failure, TSA was the most effective solution in the medium-term. Level of evidence: IV

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.

Ferreira and colleagues (2018) performed a systematic review of the viscosupplementation effectiveness with HA in the articular TMDs clinical management. Electronic searches were performed in the following databases: Medline (via PubMed), Scopus, Web of Science, Cochrane Library, Embase, LILACS, BBO, SIGLE (System for Information on Grey Literature in Europe), ClinicalTrials.gov, and the Brazilian Clinical Trials Registry (ReBec). Only randomized clinical trials that evaluated the intra-articular administration of HA or its derivatives in OA and/or anterior displacement of the TMJ disc were included. The primary outcomes evaluated were patients' self-report of pain and/or discomfort in the TMJ. Each study was assessed for the risk of bias, using the Cochrane collaboration's risk of bias tool. A total of 640 studies were obtained in the electronic search. After the application of the eligibility criteria, manual search, and duplicate removal, 21 articles were included; 5 articles classified their volunteers with internal derangements of the TMJ, in 4 articles the treatment was directed to participants with disc displacement with reduction and the other articles evaluated HA therapy in OA. The protocols presented heterogeneity, varying in the form of application, associated or not with arthrocentesis, number of applications, molecular weight, dose and concentration; 9 studies presented high risk of bias. The authors concluded that due to the heterogeneity and methodological inconsistencies of the studies evaluated, it was not possible to establish the efficacy of HA in articular TMDs.

In a randomized clinical trial, Castano-Joaqui and colleagues (2021) examined the effects of HA as an adjunct to TMJ arthroscopy, relative to standard TMJ arthroscopy, in Wilkes stage-III and stage-IV patients. A total of 51 patients were allocated to a TMJ arthroscopy (n = 25) or a TMJ arthroscopy plus HA (n = 26) group; VAS joint pain scores, maximum mouth opening (MMO), and muscle pain were measured at baseline, and at 3, 6, 9, and 12 months. Disk position on magnetic resonance imaging (MRI) was examined at baseline and 12 months. Oral health-related QOL (OHR-QOL) was assessed at baseline, and at 6 and 12 months. No group differences were observed in clinical or radiographic measurements ($p \geq 0.05$). The results did not indicate any benefit of HA

as an adjuvant therapy to arthroscopy during follow-up months 3 to 12. TMJ arthroscopy improved OHR-QOL at 6 and 12 months (Oral Health Impact Profile-14 questionnaire scores of -14.59 and -14.27, 95 % CI: -17.55 to -11.63 and -17.27 to -11.27), respectively, as well as pain and MMO, at all follow-up time-points ($p < 0.001$). The authors concluded that beneficial effect of HA injection during TMJ arthroscopy after the 3-month follow-up was not observed.

Treatment of First Metatarsophalangeal Osteoarthritis (Hallux Rigidus)

In an observational, open-label, single-arm, pilot study, Galois et al (2022) examined the safety and short-term effectiveness of a single IA injection of mannitol-modified cross-linked HA (HANOX-M-XL) in patients with painful 1st metatarsophalangeal joint OA (1stMTPJ-OA). The was a prospective, multi-center trial, with a 3-month follow-up. Inclusion criteria were patients with symptomatic 1st MTPJ-OA not relieved by analgesics and/or NSAIDs and/or foot orthotic. All subjects received a single, imaging-guided (IA injection of 1-ml of HANOX-M-XL in the 1st MTPJ. The primary outcome was the change in pain between the date of injection and month 3. The secondary outcomes were the patient assessment of effectiveness, the decrease in pain killer use and the influence of the radiographic score on the clinical effectiveness. A total of 65 subjects (72.3 % women, mean age of 60 years) were included in the trial. Coughlin-Shurnas radiological grade was 1 in 28 patients, 2 in 29, and 3 in 6. At baseline and month 3, the average pain (0 to 10) was 6.5 ± 1.8 and 2.8 ± 2.3, respectively. The change in pain score was highly significant (-3.1 ± 2.9; $p < 0.0001$). At baseline there was no statistically significant difference in pain between the radiological stages ($p = 0.69$). At endpoint, the average pain score was 2.0 ± 1.9 in x-ray stage 1, 3.1 ± 2.3 in stage 2 and 3.3 ± 2.4 in stage 3 ($p = 0.001$). Mild-to-moderate AEs were reported by 15 patients. All were a transient increase of the hallux pain that occurred immediately and up to 6 hours after injection and resolved in 1 to 7 days. The authors concluded that the findings of this pilot study suggested that a single IA injection of HANOX-M-XL was safe and mainly benefited patients with mild moderate 1st MTPJ-OA. Moreover, these researchers stated that further RCTs with longer follow-

ups are needed to confirm these preliminary findings. The main drawbacks of this study were its non-controlled design, and short-term follow-up (3 months).

Viscoelastic Hydrogel Hymovis MO.RE. for the Treatment of Knee Osteoarthritis

Bernetti and colleagues (2021) examined the safety and effectiveness of a single IA injection (32 mg/4 ml) of a new HA derivative hydrogel (Hymovis MO.RE.) for the treatment of adult regular sports players affected by knee OA arising from overuse injuries. Patients were prospectively enrolled if they regularly practiced sports and were diagnosed with Kellgren-Lawrence grade I to III OA. Subjects received a single Hymovis MO.RE. IA injection and were examined 30, 90, 180, and 360 days thereafter. The assessment involved measuring changes in knee function, pain, the ADL, and QOL by using the KOOS, GAIT analysis, the WOMAC scores for knee pain (WOMAC A) and function (WOMAC C), and a VAS pain score. The study included 31 patients (23 women and 8 men, median age of 49 years). KOOS function sub-score, as well as GAIT cadence and velocity, showed a statistically significant increase at each time-point following injection ($p < 0.0001$). WOMAC, KOOS pain, symptoms, ADL, and QOL scores also significantly improved at all control visits. No severe AEs or treatment-related events were detected. The authors concluded that a single Hymovis MO.RE. (32 mg/4 ml) IA injection provided a rapid, lasting, and safe response in regular sports players affected by knee OA, possibly representing a viable therapeutic option for this demanding patient subgroup. Moreover, these researchers stated that further investigations including a control group are needed to confirm these findings.

The authors stated that the principal drawback of this study was its small sample size (n = 31) and the lack of a similar control group undergoing the standard treatment. Moreover, only 3 patients had a grade III KL OA; and a surface EMG was not used. Furthermore, no specific questionnaires examining sports performance were administered to patients; thus, allowing only for an indirect assessment of effects specifically concerning sports activity. This calls for large, prospective, cohort studies to further evaluate the effectiveness of this treatment in regular sports players affected by knee OA. These investigators noted

that given the clinical characteristics and expectations of this particular patient population, future studies are also needed to determine the possible preventive role of IA Hymovis MO.RE. injection in reducing knee injuries as well as its effectiveness when associated with physical rehabilitation. These researchers stated that further investigations should include GAIT assessment since it may provide objective confirmation of subjectively-measured scores, and it has been shown to be predictive of OA progression.

Viscosupplementation for Muscle Stiffness/Spastic Hemiparesis

Raghavan and colleagues (2016) noted that spasticity is a common movement disorder after neurologic injury of cerebral and spinal origin such as stroke, traumatic brain injury (TBI), brain tumor, cerebral palsy (CP), spinal cord injury (SCI), and multiple sclerosis (MS). Upper limb spasticity is associated with reduced functional independence and a 4-fold increase in direct care costs during the 1st year post-stroke. The prevalence of spasticity increases over time, contributing to further disability long after the neurologic injury. Spasticity is challenging to treat because the underlying neural and non-neural mechanisms and their interactions are not fully understood. The neural mechanism underlying spasticity is hyper-excitability of the stretch reflex due to disinhibition of cortical influences on spinal cord circuitry, which results in velocity-dependent increase in tonic stretch reflexes. However, many patients with spasticity do not show any signs of hyperreflexia. Instead, muscle stiffness, defined as increased resistance to passive movement, is the commonest presenting sign in individuals with spasticity. Muscle stiffness adds further insult to the underlying weakness. It both prevents full passive movement (leading to abnormal posturing that could become fixed over time) and makes active movement more difficult in patients who are already weak from the neurologic injury. Non-neural peripheral mechanisms are thought to cause muscle stiffness, although this has not been shown conclusively. Current therapeutic options for spasticity include oral medications such as benzodiazepines, baclofen, and tizanidine that are central nervous system (CNS) depressants used to suppress spinal hyper-excitability, and local injections of botulinum toxin (BTX) used to suppress muscle over-activity. Whereas the oral medications could produce cognitive deficits, fatigue, and muscle weakness, BTX injections produce focal muscle weakness. Therefore, it

is necessary to balance the risks and benefits of treatment, which often remains inadequate. Furthermore, these treatments do not directly address muscle stiffness. The authors proposed the “Hyaluronan Hypothesis”, which postulates that the accumulation of hyaluronan within muscles promotes the development of muscle stiffness. They reported that the enzyme hyaluronidase, which hydrolyzes hyaluronan, and is available for off-label clinical use, increases both passive and active joint movement, and reduces muscle stiffness in individuals with upper limb spasticity. These results fill a critical gap in the understanding of muscle stiffness, and present a promising treatment for a vexing and widespread problem. In this study, a total of 20 patients with unilateral upper limb spasticity received multiple intra-muscular injections of human recombinant hyaluronidase with saline at a single visit. The safety and efficacy of the injections, passive and active movement, and muscle stiffness at 8 upper limb joints were assessed at 4 time-points: pre-injection (T0), within 2 weeks (T1), within 4 to 6 weeks (T2), and within 3 to 5 months post-injection (T3). There were no clinically significant adverse effects from the injections. Passive movement at all joints, and active movement at most joints increased at T1, and persisted at T2 and T3 for most joints. The modified Ashworth scores also declined significantly over time post-injection. The authors concluded that hyaluronidase injections offered a safe and potentially effective treatment for muscle stiffness in neurologically impaired individuals. These researchers stated that a blinded, randomized, placebo-controlled trial is needed to control for a placebo response, the effects of confounding variables such as number and location of injection sites, amount and quality of therapy, and investigator bias in recording and analyzing movement. This report did not address the effect of repeated drug administration, although 15/20 patients did return for further injections. The results of this study warrant replication by independent groups. They noted that future studies should also directly examine the role of hyaluronan and hyaluronidase in changing the mechanical properties of spastic muscles using simultaneous joint angle, torque, and electromyographic measurements to tease apart the effects on spasticity versus stiffness, and examine the efficacy of treatment with hyaluronidase on improvement in motor control, prevention of muscle contracture, reduction in sensorimotor impairment, and increase in quality of life. These investigators noted that this case series provided preliminary evidence for the safety and potential efficacy of hyaluronidase injections

as a treatment for muscle stiffness that may enhance functional recovery in the spastic upper limb, and may be applicable to other disorders characterized by muscle stiffness.

Mayer (2018) presented 2 recent articles that propose novel interventions for treating spastic hemiparesis by changing biological infrastructure. In 18 patients with unilateral spastic arm paralysis due to chronic cerebral injury of greater than 5 years' duration, Zheng et al (2018) transferred the C7 nerve from the non-paralyzed side to the side of the arm that was paralyzed. Over a follow-up period of 12 months, they found greater improvement in function and a reduction of spasticity compared to rehabilitation alone. Using functional magnetic resonance imaging (fMRI), they also found evidence for physiological connectivity between the ipsilateral cerebral hemisphere and the paralyzed hand. In the 2nd article, Raghavan et al (2016) examined the concept of stiffness, a common symptom in patients with spastic hemiparesis, as a physical change in the infrastructure of muscle. Raghavan's non-neural hyaluronan hypothesis postulated that an accumulation of hyaluronan within spastic muscles promotes the development of muscle stiffness in patients with an upper motor neuron syndrome (UMNS). In a case series of 20 patients with spastic hemiparesis, Raghavan et al reported that upper limb intra-muscular injections of hyaluronidase increased passive and active joint movement and reduced muscle stiffness. The author concluded that interventions that change biological infra-structure in UMNS is a paradigm on the horizon that bears watching.

References

The above policy is based on the following references:

1. Abate M, Pulcini D, Di Iorio A, Schiavone C. Viscosupplementation with intra-articular hyaluronic acid for treatment of osteoarthritis in the elderly. Curr Pharm Des. 2010;16(6):631-640.
2. Abate M, Schiavone C, Salini V. Hyaluronic acid in ankle osteoarthritis: Why evidence of efficacy is still lacking? Clin Exp

Rheumatol. 2012;30(2):277-281.

3. Adams ME, Atkinson MH, Lussier AJ, et al. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: A Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthritis Cartilage. 1995;3(4):213-225.
4. Adams ME. An analysis of clinical studies of the use of crosslinked hyaluronan, hylan, in the treatment of osteoarthritis. J Rheumatol. 1993;39 (Suppl):16-18.
5. Adelaide Health Technology Assessment (AHTA). Intra-articular viscosupplementation for treatment of osteoarthritis of the knee. Systematic Reviews. Adelaide, SA: AHTA; 2003.
6. Agency for Healthcare Research and Quality (AHRQ). Managing osteoarthritis: Helping the elderly maintain function and mobility. AHRQ Research in Action [newsletter]. Issue 4. Rockville, MD: AHRQ; May 2002.
7. Aggarwal A, Sempowski IP. Hyaluronic acid injections for knee osteoarthritis. Systematic review of the literature. Can Fam Physician. 2004;50:249-256.
8. Allan GM, Lebrun CM. Viscosupplementation (hyaluronic acid or hylan): Cushioning the blow (to your wallet)? Tools for Practice. Edmonton, AB: Alberta College of Family Physicians; May 13, 2013.
9. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986;29(8):1039-1049.
10. American Academy of Orthopaedic Surgeons (AAOS). Clinical practice guideline on the treatment of osteoarthritis of the knee (non-arthroplasty). Rosemount, IL: AAOS; December 2008.
11. American Academy of Orthopaedic Surgeons (AAOS). Treatment of osteoarthritis of the knee. 2nd ed. Summary of Recommendations. Rosemount, IL: AAOS; 2013.
12. American Academy of Orthopaedic Surgeons/American Association of Neurological Surgeons/American College of Rheumatology/American College of Physical Medicine and

Rehabilitation. Clinical Guideline on Knee Pain. Rosemont, IL: American Academy of Orthopaedic Surgeons; 1996.

13. American College of Occupational and Environmental Medicine (ACOEM). Knee disorders. In: Hegmann KT, editor(s). Occupational medicine practice guidelines. Evaluation and management of common health problems and functional recovery in workers. 3rd ed. Elk Grove Village, IL: ACOEM; 2011.
14. American College of Occupational and Environmental Medicine (ACOEM). Hand, wrist, and forearm disorders not including carpal tunnel syndrome. In: Hegmann KT, editor(s). Occupational medicine practice guidelines. Evaluation and management of common health problems and functional recovery in workers. 3rd ed. Elk Grove Village, IL: ACOEM; 2011.
15. American College of Rheumatology, Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum. 2000;43(9):1905-1915.
16. Anika Therapeutics, Inc. Orthovisc high molecular weight hyaluronan. Prescribing Information. Bedford, MA: Anika Therapeutics; September 2016.
17. Anika Therapeutics. Monovisc. Prescribing Information. Bedford, MA: Anika Therapeutics; July 2020.
18. Arrich J, Piribauer F, Mad P, et al. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: Systematic review and meta-analysis. CMAJ. 2005;127(8):1039-1043.
19. Bahadir C, Onal B, Dayan VY, Gürer N. Comparison of therapeutic effects of sodium hyaluronate and corticosteroid injections on trapeziometacarpal joint osteoarthritis. Clin Rheumatol. 2009;28(5):529-533.
20. Balazs EA, Denlinger JL. Viscosupplementation: A new concept in the treatment of osteoarthritis J Rheumatol Suppl. 1993;39:3-9.
21. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019;27(11):1578-1589.
22. Bellamy N, Campbell J, Robinson V, et al. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2005;(2):CD005321.
23. Bellamy N, Campbell J, Robinson V, et al. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane

Database Syst Rev. 2006;(2):CD005321.

24. Benazzo F, Perticarini L, Padolino A, et al. A multi-centre, open label, long-term follow-up study to evaluate the benefits of a new viscoelastic hydrogel (Hymovis®) in the treatment of knee osteoarthritis. Eur Rev Med Pharmacol Sci. 2016;20(5):959-968.
25. Bernetti A, Agostini F, Alviti F, et al. New viscoelastic hydrogel Hymovis MO.RE. Single intra-articular injection for the treatment of knee osteoarthritis in sportsmen: Safety and efficacy study results. Front Pharmacol. 2021;12:673988.
26. Bioventus LLC. Durolane. Instructions for Use. Durham, NC; Bioventus; November 2017.
27. Bioventus LLC. Durolane. Prescribing Information. Durham, NC: Bioventus; November 2017.
28. Bioventus LLC. GelSyn-3. Prescribing Information. Durham, NC; Bioventus; December 2017.
29. Bioventus LLC. Supartz (sodium hyaluronate). Prescribing information. Durham, NC: Bioventus; revised April 2015.
30. Bioventus, LLC. Bioventus launches Supartz FX now with expanded safety label for repeat injection cycles in knee osteoarthritis. Press Release. Durham, NC: Bioventus; October 12, 2015.
31. Bioventus, LLC. Supartz FX (sodium hyaluronate). Prescribing Information. Durham, NC: Bioventus; revised April 2015.
32. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Special report: Intra-articular hyaluronan for osteoarthritis of the knee. TEC Assessment Program. Chicago, IL: BCBSA; February 2005;19(17).
33. Brander V, Skrepnik N, Petrella RJ, et al. Evaluating the use of intra-articular injections as a treatment for painful hip osteoarthritis: A randomized, double-blind, multicenter, parallel-group study comparing a single 6-mL injection of hylan G-F 20 with saline. Osteoarthritis Cartilage. 2019;27(1):59-70.
34. Caborn D, Rush J, Lanzer W, et al. A randomized, single-blind comparison of the efficacy and tolerability of hylan G-F 20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee. J Rheumatol. 2004;31(2):333-343.
35. Carpenter B, Motley T. The role of viscosupplementation in the ankle using hylan G-F 20. J Foot Ankle Surg. 2008;47(5):377-384.

36. Carrabba M, Paresce E, Angeline M, et al. The safety and efficacy of different dose schedules of hyaluronic acid in the treatment of painful osteoarthritis of the knee with joint effusions. Eur J Rheumatol Inflamm. 1995;15(1):25-31.
37. Castano-Joaqui OG, Cano-Sanchez J, Campo-Trapero J, et al. TMJ arthroscopy with hyaluronic acid: A 12-month randomized clinical trial. Oral Dis. 2021;27(2):301-311.
38. Cleary M, Keating C, Poynton AR. Viscosupplementation in lumbar facet joint arthropathy: A pilot study. J Spinal Disord Tech. 2008;21(1):29-32.
39. Clementi D, D'Ambrosi R, Bertocco P, et al. Efficacy of a single intra-articular injection of ultra-high molecular weight hyaluronic acid for hip osteoarthritis: A randomized controlled study. Eur J Orthop Surg Traumatol. 2018;28(5):915-922.
40. Colorado Division of Workers' Compensation. Cumulative trauma conditions medical treatment guidelines. Denver, CO: Colorado Division of Workers' Compensation; September 16, 2010.
41. Conrozier T, Bozgan AM, Bossert M, et al. Standardized follow-up of patients with symptomatic knee osteoarthritis treated with a single intra-articular injection of a combination of cross-linked hyaluronic acid and mannitol. Clin Med Insights Arthritis Musculoskelet Disord. 2016;9:175-179.
42. Conrozier T, Couris CM, Mathieu P, et al. Safety, efficacy and predictive factors of efficacy of a single intra-articular injection of non-animal-stabilized-hyaluronic-acid in the hip joint: Results of a standardized follow-up of patients treated for hip osteoarthritis in daily practice. Arch Orthop Trauma Surg. 2009;129(6):843-848.
43. Conrozier T, Vignon E. Is there evidence to support the inclusion of viscosupplementation in the treatment paradigm for patients with hip osteoarthritis? Clin Exp Rheumatol. 2005;23(5):711-716.
44. 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 biochemical evaluations. Eur J Rheumatol Inflamm. 1995;15:47-56.
45. Creamer P. Intra-articular corticosteroid injections in osteoarthritis; do they work and if so, how? Ann Rhemuatic Dis. 1997:56:634-636.
46. Dagenais P, Framarin A. Viscosupplementation for the treatment of osteoarthrits of the knee. Summary. AETMIS 07-06. Montreal,

QC: Agence d'evaluation des technologies et des modes d'intervention en sante (AETMIS); July 2007.
47. 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.
48. Dagenais S. Intra-articular hyaluronic acid (viscosupplementation) for hip osteoarthritis. Issues in Emerging Health Technologies Issue 98. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); 2007.
49. de Campos GC, Rezende MU, Pailo AF, et al. Adding triamcinolone improves viscosupplementation: A randomized clinical trial. Clin Orthop Relat Res. 2013;471(2):613-620.
50. De Lucia O, Jerosch J, Yoon S, et al. One-year efficacy and safety of single or one to three weekly injections of hylan G-F 20 for knee osteoarthritis: A systematic literature review and meta-analysis. Clin Rheumatol. 2021;40(6):2133-2142.
51. de Rezende MU, Rosa TB, Pasqualin T, et al. Subjective results of joint lavage and viscosupplementation in hemophilic arthropathy. Acta Ortop Bras. 2015;23(3):162-166.
52. Deveza LA. Overview of the management of osteoarthritis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed October 2020.
53. Devulder J, Deene P, De Laat M, et al. Nerve root sleeve injections in patients with failed back surgery syndrome: A comparison of three solutions. Clin J Pain. 1999;15(2):132-135.
54. Devulder J. Transforaminal nerve root sleeve injection with corticosteroids, hyaluronidase, and local anesthetic in the failed back surgery syndrome. J Spinal Disord. 1998;11(2):151-154.
55. Di Martino A, Tentoni F, Di Matteo B, et al. Early viscosupplementation after anterior cruciate ligament reconstruction: A randomized controlled trial. Am J Sports Med. 2016;44(10):2572-2578.
56. Dougados M, Nguyen M, Listrat V, et al. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: A 1 year placebo-controlled trial. Osteoarthritis Cartilage. 1993;1(2):97-103.
57. Duymus TM, Mutlu S, Dernek B, et al. Choice of intra-articular injection in treatment of knee osteoarthritis: Platelet-rich plasma,

hyaluronic acid or ozone options. Knee Surg Sports Traumatol Arthrosc. 2017;25(2):485-492.

58. Espallargues M, Pons JM. Efficacy and safety of viscosupplementation with Hylan G-F 20 for the treatment of knee osteoarthritis: A systematic review. Int J Technol Assess Health Care. 2003;19(1):41-56.
59. Evanich JD, Evanich CJ, Wright MB, Rydlewicz JA. Efficacy of intraarticular hyaluronic acid injections in knee osteoarthritis. Clin Orthop. 2001;(390):173-181.
60. Fernandez Lopez J-C, Ruano-Ravina A. Efficacy and safety of hyaluronic acid (technical report) [summary]. CT2005/06. Santiago de Compostela, Spain: Galician Agency for Health Technology Assessment (AVALIA-T); 2005.
61. Fernandez Lopez JC, Ruano-Ravina A. Efficacy and safety of intraarticular hyaluronic acid in the treatment of hip osteoarthritis: A systematic review. Osteoarthritis Cartilage. 2006;14(12):1306-1311.
62. Ferreira N, Masterson D, Lopes de Lima R, et al. Efficacy of viscosupplementation with hyaluronic acid in temporomandibular disorders: A systematic review. J Craniomaxillofac Surg. 2018;46(11):1943-1952.
63. Ferring Pharmaceuticals Inc. Euflexxa (1% sodium hyaluronate). Prescribing Information. 6309501103. Parsippany, NJ; revised July 2016.
64. Fidia Pharma USA Inc. Hymovis (hyaluronic acid) Prescribing Information. Florham Park, NJ: Fida Pharma USA; revised June 2021.
65. Fidia Pharma USA, Inc. Hyalgan (sodium hyaluronate). Prescribing information. Florham Park, NJ: Fidia Pharma USA; revised August 2017.
66. Fidia Pharma USA, Inc. Triluron. Prescribing Information. Florham Park, NJ: Fida Pharma; revised July 2019.
67. Filardo G, Di Matteo B, Tentoni F, et al. No effects of early viscosupplementation after arthroscopic partial meniscectomy: A randomized controlled trial. Am J Sports Med. 2016;44(12):3119-3125.
68. Finn BC, Young P, Laborde H, et al. Palindromic rheumatism. Report of one case. Rev Med Chil. 2010;138(7):852-855.

69. Formiguera SSE. Intra-articular hyaluronic acid in the treatment of osteoarthritis of the knee: A short-term study. Eur J Rheumatol Inflamm. 1995;15:33-38.
70. Fuchs S, Monikes R, Wohlmeiner A, Heyse T. Intra-articular hyaluronic acid compared with corticoid injections for the treatment of rhizarthrosis. Osteoarthritis Cartilage. 2006;14(1):82-88.
71. Galois L, Coillard J-Y, Porterie J, et al. Open-label pilot study of a single intra-articular injection of mannitol-modified cross-linked hyaluronic acid (HANOX-M-XL) for the treatment of the first metatarsophalangeal osteoarthritis (hallux rigidus): The REPAR Trial. Clin Med Insights Arthritis Musculoskelet Disord. 2022;15:11795441211055882.
72. Genovese MC. Joint and soft-tissue injection. A useful adjuvant to systemic and local treatment. Postgrad Med. 1998;103(2):125-134.
73. Genzyme Biosurgery. Synvisc (Hylan G-F 20). Prescribing Information. Ridgefield, NJ; revised May 2023.
74. Genzyme Biosurgery. Synvisc-One (Hylan G-F 20). Prescribing Information. Ridgefield, NJ; revised May 2023.
75. Giombini G, Menotti F, Di Cesare A, et al. Comparison between intrarticular injection of hyaluronic acid, oxygen ozone, and the combination of both in the treatment of knee osteoarthrosis. J Biol Regul Homeost Agents. 2016;30(2):621-625.
76. Goiato MC, da Silva EV, de Medeiros RA, et al. Are intra-articular injections of hyaluronic acid effective for the treatment of temporomandibular disorders? A systematic review. Int J Oral Maxillofac Surg. 2016;45(12):1531-1537.
77. Graf J, Neusel E, Schneider E, et al. Intra-articular treatment with hyaluronic acid in osteoarthritis of the knee joint: A controlled clinical trial versus mucopolysaccharide polysulfuric acid ester. Clin Exp Rheumatol. 1993;11(4):367-372.
78. Grogan KA, Chang TJ, Salk RS. Update on viscosupplementation in the treatment of osteoarthritis of the foot and ankle. Clin Podiatr Med Surg. 2009;26(2):199-204.
79. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis

of the hand, hip, and knee. Arthritis Care Res. 2012;64(4):465-474.

80. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. Rheumatology (Oxford). 1999;38(7):602-607.
81. Izquierdo R, Voloshin I, Edwards S, et al; American Academy of Orthopedic Surgeons. Treatment of glenohumeral osteoarthritis. J Am Acad Orthop Surg. 2010;18(6):375-382.
82. Johnston C. AAOS: Hylan injections show equal efficacy as corticosteroid for arthritis of the knee [news]. Doctors Guide Global Edition. Montreal, QC: P/S/L Group and Doctor's Guide Publishing Limited; February 7, 2003.
83. Jordan KM, Arden NK, Doherty M, et al. EULAR recommendations 2003: An evidence based approach to the management of knee osteoarthritis: report of a task force of the standing committee for international clinical studies including therapeutic trials (ESCISIT). Ann Rheum Dis. 2003;62:1145-1155.
84. Jüni P, Reichenbach S, Trelle S, et al; Swiss Viscosupplementation Trial Group. Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: A randomized controlled trial. Arthritis Rheum. 2007;56(11):3610-3619.
85. Kany J, Benkalfate T, Favard L, et al; French Society for Shoulder, Elbow (SOFEC). Osteoarthritis of the shoulder in under-50 year-olds: A multicenter retrospective study of 273 shoulders by the French Society for Shoulder and Elbow (SOFEC). Orthop Traumatol Surg Res. 2021;107(1):102756.
86. Kirwan JR, Rankin E. Intra-articular therapy in osteoarthritis. Baillieres Clin Rheumatol. 1997;11(4):769-794.
87. Kolasinski SL, Tuhina N, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guidelines for the management of osteoarthritis of the hand, hip, and knee. Arthritis Rheumatol. 2020;72(2):220-233.
88. Kotz R, Kolarz G. Intra-articular hyaluronic acid: Duration of effect and results of repeated treatment cycles. Am J Orthop. 1999;28(11 suppl):5-7.
89. Lee G-W, Kwak W-K, Lee K-B. Effects and safety of intra-articular sodium hyaluronate injection for the treatment of ankle osteoarthritis: A prospective clinical trial. J Foot Ankle Surg. 2022;61(2):345-349..

90. Leite VF, Daud Amadera JE, Buehler AM. Viscosupplementation for hip osteoarthritis: A systematic review and meta-analysis of the efficacy on pain and disability, and the occurrence of adverse events. Arch Phys Med Rehabil. 2018;99(3):574-583.
91. Letizia Mauro G, Sanfilippo A, Scaturro D. The effectiveness of intra-articular injections of Hyalubrix® combined with exercise therapy in the treatment of hip osteoarthritis. Clin Cases Miner Bone Metab. 2017;14(2):146-152.
92. Letizia Mauro G, Scaturro D, Sanfilippo A, Benedetti MG. Intra-articular hyaluronic acid injections for hip osteoarthritis. J Biol Regul Homeost Agents. 2018;32(5):1303-1309.
93. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: A meta-analysis. JAMA. 2003;290(23):3115-3121.
94. Lohmander LS, Dalen N, Englund G, H, et al. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: A randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. Ann Rheum Dis. 1996;55(7):424-431.
95. Lussier A, Cividino AA, McFarlane CA, et al. Viscosupplementation with hylan for the treatment of osteoarthritis: Findings from clinical practice in Canada. J Rheumatol. 1996;23(9):1579-1585.
96. Maheu E, Ayral X, Dougados M. A hyaluronan preparation (500-730 kDa) in the treatment of osteoarthritis: A review of clinical trials with Hyalgan. Int J Clin Pract. 2002;56(10):804-813.
97. Manfredini D, Piccotti F, Guarda-Nardini L. Hyaluronic acid in the treatment of TMJ disorders: A systematic review of the literature. Cranio. 2010;28(3):166-176.
98. Mao B, Pan Y, Zhang Z, et al. Efficacy and safety of hyaluronic acid intra-articular injection after arthroscopic knee surgery: A systematic review and meta-analysis. Orthop Surg. 2023;15(1):16-27.
99. Maricar N, Parkes MJ, Callaghan MJ, et al. Where and how to inject the knee—A systematic review. Semin Arthritis Rheum. 2013;43(2):195-203.
100. Mayer NH. New treatment approaches on the horizon for spastic hemiparesis. PM R. 2018;10(9S2):S144-S150.
101. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee

Osteoarthritis Cartilage. 2014;22(3):363-88.

102. McPoil TG, Martin RL, Cornwall MW, et al. Heel pain -- plantar fasciitis: Clinical practice guidelines linked to the International Classification of Function, Disability, and Health from the Orthopaedic Section of the American Physical Therapy Association. J Orthop Sports Phys Ther. 2008;38(4):A1-A18.
103. Medical Services Advisory Committee (MSAC). Intra-articular viscosupplementation for treatment of osteoarthritis of the knee. MSAC Application 1045. Canberra, ACT: MSAC; 2003.
104. Migliore A, Giovannangeli F, Bizzi E, et al. Viscosupplementation in the management of ankle osteoarthritis: A review. Arch Orthop Trauma Surg. 2011;131(1):139-147.
105. Migliore A, Massafra U, Bizzi E, et al. Duration of symptom relief after intra-articular injection of hyaluronic acid combined with sorbitol (anti-ox-vs) in symptomatic hip osteoarthritis. Int J Immunopathol Pharmacol. 2014;27(2):245-252.
106. Migliore A, Tormenta S, Martin Martin LS, et al. The symptomatic effects of intra-articular administration of hylan G-F 20 on osteoarthritis of the hip: Clinical data of 6 months follow-up. Clin Rheumatol. 2006;25(3):389-393.
107. Migliore A, Tormenta S, Valente C, et al. Intra-articular treatment with Hylan G-F 20 under ultrasound guidance in hip osteoarthritis. Clinical results after 12 months follow-up. Reumatismo. 2005;57(1):36-43.
108. Munteanu SE, Zammit GV, Menz HB, et al. Effectiveness of intra-articular hyaluronan (Synvisc, hylan G-F 20) for the treatment of first metatarsophalangeal joint osteoarthritis: A randomised placebo-controlled trial. Ann Rheum Dis. 2011;70(10):1838-1841.
109. National Clinical Guideline Centre. Osteoarthritis. Care and management in adults. Clinical Guideline CG 177. Methods, evidence and recommendations. London, UK: National Institute for Health and Care Excellence; February 2014.
110. National Institute for Health and Clinical Excellence (NICE). Osteoarthritis. The Care and Management of Osteoarthritis in Adults. NICE Clinical Guideline 59. London, UK: NICE; February 2008.
111. Neustadt DH. Intra-articular injections for osteoarthritis of the knee. Cleve Clin J Med. 2006;73(10):897-911.

112. Neustadt DH. Long-term efficacy and safety of intra-articular sodium hyaluronate (Hyalgan) in patients with osteoarthritis of the knee. Clin Exp Rheumatol. 2003;21(3):307-311.
113. Ometti M, Schipani D, Conte P, et al. The efficacy of intra-articular HYADD4-G injection in the treatment of femoroacetabular impingement: Results at one year follow up. J Drug Assess. 2020;9(1):159-166.
114. Ontario Ministry of Health and Long-Term Care, Medical Advisory Secretariat. Intra-articular viscosupplementation with hylan G-F 20 to treat osteoarthritis of the knee. Health Technology Literature Review. Toronto, ON: Ontario Ministry of Health and Long-Term Care; 2005:1-67.
115. OrthogenRx Inc. GenVisc 850. Prescribing Information. Doylestown, PA: OrthogenRx; November 2019.
116. OrthogenRx, Inc. TriVisc (sodium hyaluronate). Full Prescribing Information. Doylestown, PA: OrthogenRx; November 2019.
117. Pagnano M, Westrich G. Successful nonoperative management of chronic osteoarthritis pain of the knee: Safety and efficacy of retreatment with intra-articular hyaluronans. Osteoarthritis Cartilage. 2005;13(9):751-761.
118. Palco M, Fenga D, Basile GC, et al. Platelet-rich plasma combined with hyaluronic acid versus leucocyte and platelet-rich plasma in the conservative treatment of knee osteoarthritis. A retrospective study. Medicina (Kaunas). 2021;57(3):232.
119. Palmieri B, Rottigni V, Iannitti T. Preliminary study of highly cross-linked hyaluronic acid-based combination therapy for management of knee osteoarthritis-related pain. Drug Des Devel Ther. 2013;7:7-12.
120. Pleimann JH, Davis WH, Cohen BE, Anderson RB. Viscosupplementation for the arthritic ankle. Foot Ankle Clin. 2002;7(3):489-494.
121. Quarterman JC, Naguib YW, Chakka JL, et al. HPLC-UV method validation for amobarbital and pharmaceutical stability evaluation when dispersed in a hyaluronic acid hydrogel: A new concept for post-traumatic osteoarthritis prevention. J Pharm Sci. 2022;111(5):1379-1390.
122. Raghavan P, Lu Y, Mirchandani M, Stecco A. Human recombinant hyaluronidase injections for upper limb muscle stiffness in

individuals with cerebral injury: A case series. EBioMedicine. 2016;9:306-313.

123. Ridenour S, Reader A, Beck M, Weaver J. Anesthetic efficacy of a combination of hyaluronidase and lidocaine with epinephrine in inferior alveolar nerve blocks. Anesth Prog. 2001;48(1):9-15.
124. Rosenberg JN, Corticosteroid injections of joints and soft tissues. eMedicine Physical Medicine and Rehabilitation Topic 211. Omaha, NE: eMedicine.com; updated September 14, 2001.
125. Roux C, Fontas E, Breuil V, et al. Injection of intra-articular sodium hyaluronidate (Sinovial) into the carpometacarpal joint of the thumb (CMC1) in osteoarthritis. A prospective evaluation of efficacy. Joint Bone Spine. 2007;74(4):368-372.
126. Russo F, D'Este M, Vadalà G, et al. Platelet rich plasma and hyaluronic acid blend for the treatment of osteoarthritis: Rheological and biological evaluation. PLoS One. 2016;11(6):e0157048.
127. Rutjes AW, Juni P, da Costa BR, et al. Viscosupplementation for osteoarthritis of the knee: A systematic review and meta-analysis. Ann Intern Med. 2012;157(3):180-191.
128. Salini V, De Amicis D, Abate M, et al. Ultrasound-guided hyaluronic acid injection in carpometacarpal osteoarthritis: Short-term results. Int J Immunopathol Pharmacol. 2009;22(2):455-460.
129. Salk R, Chang T, D'Costa W, et al. Viscosupplementation (hyaluronans) in the treatment of ankle osteoarthritis. Clin Podiatr Med Surg North Am. 2005;22(4):585-597, vii.
130. Salk RS, Chang TJ, D'Costa WF, et al. Sodium hyaluronate in the treatment of osteoarthritis of the ankle: A controlled, randomized, double-blind pilot study. J Bone Joint Surg Am. 2006;88(2):295-302.
131. Samson DJ, Grant MD, Ratko TA, et al. Treatment of primary and secondary osteoarthritis of the knee. Evidence Report/Technology Assessment No. 157. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2007.
132. Scali JJ. Intra-articular hyaluronic acid in the treatment of osteoarthritis of the knee: A long term study. Eur J Rheumatol Inflamm. 1995;15(1):57-62.
133. Scott D, Kowalczyk A. Osteoarthritis of the knee. In: BMJ Clinical Evidence. London, UK: BMJ Publishing Group; October 2006.

134. Shi Z, Guo C, Awad M. Hyaluronate for temporomandibular joint disorders. Cochrane Database Syst Rev. 2003;(1):CD002970.
135. Silva JIS, Jr, Rahal SC, Santos IFC, et al. Use of reticulated hyaluronic acid alone or associated with ozone gas in the treatment of osteoarthritis due to hip dysplasia in dogs. Front Vet Sci. 2020;7:265.
136. Singhal S, Zahid M. Palindromic rheumatism. J Indian Med Assoc. 2002;100(3):200-202.
137. Sowerby Centre for Health Informatics at Newcastle (SCHIN). Prodigy Guidance - Osteoarthritis. Prodigy: Practical Support for Clinical Governance. Newcastle upon Tyne, UK: SCHIN; revised April 2003.
138. Stahl S, Karsh-Zafrir I, Ratzon N, Rosenberg N. Comparison of intraarticular injection of depot corticosteroid and hyaluronic acid for treatment of degenerative trapeziometacarpal joints. J Clin Rheumatol. 2005;11(6):299-302.
139. Sun SF, Chou YJ, Hsu CW, Chen WL. Hyaluronic acid as a treatment for ankle osteoarthritis. Curr Rev Musculoskelet Med. 2009;2(2):78-82.
140. Tamir E, Robinson D, Koren R, et al. Intra-articular hyaluronan injections for the treatment of osteoarthritis of the knee: A randomized, double blind, placebo controlled study. Clin Exp Rheumatol. 2001;19(3):265-270.
141. Telikicherla M, Kamath SU. Accuracy of needle placement into the intra-articular space of the knee in osteoarthritis patients for viscosupplementation. J Clin Diagn Res. 2016;10(2):RC15-RC17.
142. Teva Pharmaceuticals USA, Inc. Synojoynt. Prescribing Information. North Wales, PA: Teva; March 2019.
143. Thomas JL, Christensen JC, Kravitz SR, et al; American College of Foot and Ankle Surgeons heel pain committee. The diagnosis and treatment of heel pain: A clinical practice guideline-revision 2010. J Foot Ankle Surg 2010;49(3 Suppl):S1-S19.
144. Tripathy SK, Varghese P, Behera H, et al. Intraarticular viscosupplementation following arthroscopic anterior cruciate ligament reconstruction: A systematic review. J Clin Orthop Trauma. 2022;28:101847.
145. U.S. Food and Drug Administration (FDA). TriViscTM (sodium hyaluronate). Summary of Safety and Effectiveness Data (SSED).

Premarket Approval Application (PMA) No. P160057. Silver Spring, MD: FDA; November 13, 2017.

146. van Brakel RW, Eygendaal D. Intra-articular injection of hyaluronic acid is not effective for the treatment of post-traumatic osteoarthritis of the elbow. Arthroscopy. 2006;22(11):1199-1203.
147. van den Bekerom MP, Lamme B, Sermon A, Mulier M. What is the evidence for viscosupplementation in the treatment of patients with hip osteoarthritis? Systematic review of the literature. Arch Orthop Trauma Surg. 2008;128(8):815-823.
148. Vanelli R, Costa P, Rossi SM, Benazzo F. Efficacy of intra-articular polynucleotides in the treatment of knee osteoarthritis: A randomized, double-blind clinical trial. Knee Surg Sports Traumatol Arthrosc. 2010;18(7):901-907.
149. Vannabouathong C, Del Fabbro G, Sales B, et al. Intra-articular injections in the treatment of symptoms from ankle arthritis: A systematic review. Foot Ankle Int. 2018;39(10):1141-1150.
150. Venable PJW, Maini RN. Clinical features of rheumatoid arthritis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed November 2013.
151. Washington State Department of Labor and Industries, Office of the Medical Director. Hyaluronic acid. Treatment of osteoarthritis of the knee. Technology Assessment. Olympia, WA: Washington State Department of Labor and Industries; August 1998.
152. Yoon KH, Wan WS, Kim Y-S, Park J-Y. The efficacy of intraarticular viscosupplementation after arthroscopic partial meniscectomy: A randomized controlled trial. BMC Musculoskelet Disord. 2022;23(1):32.
153. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage. 2008;16(2):137-162.
154. Zheng MX, Hua XY, Feng JT, et al. Trial of contralateral seventh cervical nerve transfer for spastic arm paralysis. N Engl J Med. 2018;378(1):22-34.
155. Zimmer. Gel-One Cross-linked Hyaluronate. Prescribing Information. 6LA40200. Warsaw, IN: Zimmer; issued May 20, 2011.

156. Zimmer, Inc. Visco-3. Prescribing Information. Warsaw, IN: Zimmer; May 2017.