Protocol

Intra-Articular Hyaluronan Injections for Osteoarthritis

(20131)

Medical Benefit		**Effective Date**: 04/01/20	**Next Review Date**: 01/21
Preauthorization	No	**Review Dates**: 01/13, 01/14, 01/15, 01/16, 01/17, 01/18, 01/19, 01/20	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With osteoarthritis of the knee	Interventions of interest are: • Intra-articular hyaluronan injections	Comparators of interest are: • Physical therapy • Medication • Surgery	Relevant outcomes include: • Symptoms • Functional outcomes • Treatment-related morbidity
Individuals: • With osteoarthritis of joints other than the knee	Interventions of interest are: • Intra-articular hyaluronan injections	Comparators of interest are: • Physical therapy • Medication • Surgery	Relevant outcomes include: • Symptoms • Functional outcomes • Treatment-related morbidity

DESCRIPTION

Intra-articular (IA) injection of hyaluronan into osteoarthritic joints is proposed to reduce pain and improve function. It is thought to replace endogenous hyaluronan and restore the viscoelastic properties of the synovial fluid. Most studies to date have assessed hyaluronan injections for knee osteoarthritis (OA), and this is the U.S. Food and Drug Administration-approved indication. Other joints (e.g., hip, shoulder) are being investigated for IA hyaluronan treatment of OA.

SUMMARY OF EVIDENCE

For individuals who have OA of the knee who receive IA hyaluronan injections, the evidence includes randomized controlled trials (RCTs) and systematic reviews of RCTs. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. Many RCTs have been published over the last two decades. While outcomes of these RCTs have been mixed, the RCT evidence base is characterized by studies showing small treatment effects of IA hyaluronan injections. In many cases, these trials are at risk of bias, and it cannot be determined with certainty whether there is a true treatment effect or whether the reported differences are due to bias. Meta-analyses of RCTs have also had mixed findings. Some meta-analyses estimating the magnitude of treatment benefit have concluded there is no clinically significant benefit; others have concluded there is a clinically significant benefit. These meta-analyses have also highlighted the limitations of this evidence base, most notably publication bias and small trial bias. For example, a meta-analysis (2016) found more than a three-fold

larger treatment effect in small trials than in larger trials (i.e., >100 participants). Overall, given the lack of a definitive treatment benefit despite a large quantity of literature, and given the biases present in the available evidence, it is unlikely there is a treatment benefit that is clinically meaningful. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who have OA of joints other than the knee who receive IA hyaluronan injections, the evidence includes RCTs, systematic reviews of RCTs, and observational studies. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. Meta-analyses of RCTs either have not found statistically significant benefits of the procedure on health outcomes or have found benefits that were statistically, but likely not clinically, significant (e.g., 0.27-point improvement on a 10-point visual analog scale for hip OA). The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Intra-articular hyaluronan injections of the knee are considered **not medically necessary**.

Intra-articular hyaluronan injections are considered **investigational** for all other joints.

MEDICARE ADVANTAGE

Purified natural hyaluronans have been approved by the FDA and may be considered **medically necessary** for the treatment of pain associated with osteoarthritis of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics.

In addition to the FDA approved use, hyaluronans may be considered **medically necessary** as a therapeutic option for osteoarthritis of the shoulder.

A repeat series of injections* (see Medicare Advantage Policy Guidelines) is considered **medically necessary** under the following circumstances:

1. The indications above continue to be met; and
2. Significant improvement in pain and functional capacity from the previous series of injections has been documented in the medical record; and
3. The last injection (in a prior course) was given at least six (6) months ago.

An injection (Synvisc-One™, Gel-One®, Durolane®) or course of the injections (Synvisc®, Hyalgan®, Supartz® or Visco-3™, Euflexxa™, Orthovisc®, GelSyn-3™, GenVisc® 850, Hymovis®, TriVisc™) will be considered **not medically necessary** if repeated within six months' time.

MEDICARE ADVANTAGE POLICY GUIDELINES

*It is recommended that repeat injections for shoulder arthritis are limited to a single repeat course.

The dose and frequency of administration should be consistent with the FDA approved labeling.

Documentation of subsequent courses of treatment must clearly establish reduction of patient symptomatology and medication usage.

BACKGROUND

KNEE OSTEOARTHRITIS

Knee osteoarthritis (OA) is common, costly, and a cause of substantial disability. Among U.S. adults, the most common causes of disability are arthritis and rheumatic disorders.

Treatment

Currently, no curative therapy is available for OA, and thus the overall goals of management are to reduce pain, disability, and the need for surgery.

Intra-articular (IA) injection of hyaluronan has been proposed as a means of restoring the normal viscoelasticity of the synovial fluid in patients with OA and reducing pain and improving function. This treatment may also be called viscosupplementation. Hyaluronan is a naturally occurring macromolecule that is a major component of synovial fluid and is thought to contribute to its viscoelastic properties. Chemical crosslinking of hyaluronan increases its molecular weight; cross-linked hyaluronans are referred to as hylans. In OA, the overall length of hyaluronan chains present in cartilage and the hyaluronan concentration in the synovial fluid are decreased.

REGULATORY STATUS

Several preparations of IA hyaluronan have been approved by the U.S. Food and Drug Administration (FDA) as an alternative to nonsteroidal anti-inflammatory drug therapy in the treatment of OA of the knee: Synvisc® and Synvisc-One® (Genzyme); Gel-One® (Zimmer); Hyalgan® (Fidia); Supartz FX™ (Bioventus); Orthovisc® (Anika); Euflexxa®, previously named Nuflexxa (Savient); Monovisc® (Anika Therapeutics); Durolane® (Bioventus); and Gel-Syn™ (Institut Biochimique SA). All products are manufactured from rooster combs, except for Durolane®, Euflexxa®, Orthovisc®, Monovisc®, Gel-Syn™, and GenVisc 850, which are produced from bacterial fermentation. Also, Synvisc® undergoes additional chemical crosslinking to create hylans with increased molecular weight (6000 kDa) compared with Hyalgan® (500-730 kDa) and Supartz™ (620-1170 kDa). Monovisc® is also cross-linked with a proprietary cross-linker. The differing molecular weights of the products lead to different half-lives; the half-life of Hyalgan® or Supartz™ is estimated at 24 hours, while the half-life of Synvisc® may range up to several days.

According to manufacturers' prescribing information for Synvisc® and Euflexxa®, IA hyaluronan 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, and to simple analgesics, e.g., acetaminophen." The product inserts further indicate that Synvisc® and Euflexxa® should be injected intra-articularly into the knee joint once per week for a total of three injections over a two- to three-week period. In contrast, five weekly injections are recommended for the Hyalgan® and Supartz™ products, and three to four weekly injections are recommended for Orthovisc®. In 2009, the FDA approved the use of single-dose hylan G-F 20 (Synvisc-One®) for the treatment of OA of the knee. In 2011, the FDA approved the use of the single-dose cross-linked hyaluronate Gel-One® (also known as Gel-200) for the treatment of OA of the knee. In 2014, Monovisc® was also approved as a single-dose treatment, while Gel-Syn™ was approved as a course of three weekly injections. In 2015, GenVisc 850 was approved as a course of three weekly injections. In 2017, Durolane was approved as a single-dose treatment.

In 2000, the FDA approved removal of a precautionary statement from the package inserts for Hyalgan® and Synvisc®, which indicated that stated that the safety and efficacy of repeat courses had not been established.

FDA has not approved IA hyaluronan for joints other than the knee.

FDA product code: MOZ.

RELATED PROTOCOLS

Electrical Stimulation for the Treatment of Arthritis

Temporomandibular Joint Dysfunction

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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