Intra-Articular Hyaluronan Injections for Osteoarthritis

(20131)

Medical Benefit
Effective Date: 04/01/17
Next Review Date: 01/18

Preauthorization
No
Review Dates: 01/13, 01/14, 01/15, 01/16, 01/17

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.

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<td>• With osteoarthritis of the knee</td>
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Description

Intra-articular (IA) injection of hyaluronan into osteoarthritic joints is proposed to improve pain and function. It is thought to replace endogenous hyaluronan, restore the viscoelastic properties of the synovial fluid. Most studies to date have assessed hyaluronan injections for knee osteoarthritis, 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 osteoarthritis.

Summary of Evidence

The evidence for IA hyaluronan injections in individuals who have osteoarthritis of the knee 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 are mixed, the RCT evidence base is characterized by studies that show small treatment effects of IA hyaluronan treatment. 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 resulted in mixed findings. Some meta-analyses estimating the magnitude of treatment benefit have concluded that there is no clinically significant benefit; however, others have concluded that there is a clinically significant benefit. These meta-analyses have also highlighted the limitations of this evidence base, most notably publication bias. 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 qualitatively that the technology is unlikely to improve the net health outcome.

The evidence for IA hyaluronan injections in individuals who have osteoarthritis of joints other than the knee includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. Meta-analyses of RCTs either have not found statistically significant benefits of the technology 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). 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**

Viscosupplementation with hyaluronans may be considered **medically necessary** for osteoarthritis of the knee or shoulder joint when:

- There is radiological evidence to support the diagnosis of osteoarthritis; and
- There is adequate documentation that simple pharmacologic therapy (e.g., aspirin), or exercise and physical therapy has been tried and the patient has failed to respond satisfactorily.

A repeat series of injections 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.

**Medicare Advantage Policy Guidelines**

The following products have received FDA approval:

- Hylan G-F 20 (Synvisc®), given once weekly for a total of three weeks.
- Hylan G-F 20 (Synvics-OneTM), given once per six months and limited to osteoarthritis of the knee.
- Sodium hyaluronate (Hyalgan®, Supartz®, EuflexxaTM, Monovisc™, Gel-Syn™, GenVisc® 850).
  - Hyalgan®, given once weekly for a total of five injections.
  - Supartz®, given once a week for a total of five weeks.
  - EuflexxaTM, device indicated for a three-injection treatment regimen.
  - Monovisc™, the intra-articular injection is given once.
  - Gel-Syn™, given once weekly for three weeks.
  - GenVisc® 850, treatment cycle consists of five injections given at weekly intervals.
- High molecular weight Hyaluronan (Orthovisc®), administered weekly for three to four weeks.
- Hyaluronic acid (Gel-One®), the intra-articular injections are given once.
- High molecular weight viscoelastic hyaluronan (Hymovis®), administered two times in two injections one week apart.

**Background**

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. 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 injection of hyaluronan has been proposed as a means of restoring the normal viscoelasticity of the synovial fluid in patients with OA and improving pain and function. This treatment may also be called visco-supplementation. 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); and Gel-Syn™ (Institut Biochimique SA). All products are manufactured from rooster combs except for 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 Hylagan or Supartz is estimated at 24 hours, while the half-life of Synvisc may range up to several days.

According to the manufacturer’s prescribing information for Synvisc and Euflexxa, IA hyaluronan is “indicated for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative nonpharmacologic 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 Hylagan and Supartz products, and three to four weekly injections are recommended for Orthovisc. In February 2009, FDA approved the use of single-dose hylan G-F 20 (Synvisc-One) for the treatment of OA of the knee. In 2011, 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 2000, FDA approved removal of a precautionary statement from the package inserts for Hylagan and Synvisc that stated that the safety and efficacy of repeat courses have not been established.

FDA has not approved intra-articular hyaluronan for joints other than the knee.

FDA product code: MOZ.
Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment 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.

32. National Government Services, Inc. Local Coverage Determination (LCD): Drugs and Biologicals, Coverage of, for Label and Off-Label Uses (L33394), Revision Effective Date for services performed on or after 08/01/2016.