MEDICAL POLICY – 2.01.31
Intra-Articular Hyaluronan Injections for Osteoarthritis

BCBSA Ref. Policy: 2.01.31
Effective Date: July 1, 2017
Last Revised: June 6, 2017
Replaces: N/A

RELATED MEDICAL POLICIES:
7.01.549 Knee Arthroscopy in Adults

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Hyaluronan, or sodium hyaluronate, is a natural substance found in some joints of the human body. This substance acts as a lubricant and helps joints work better. There are also other substances similar to hyaluronan that have been used for the past ten years to treat knee pain due to osteoarthritis of the knee. These substances have been manufactured to be injected into the knee one or more times. Early studies suggested the injections helped decrease pain. During the past 5 years, re-analysis of the best early medical studies which included thousands of patients have shown that these injections do not offer significant relief for most people. Some professional societies recommend that these injections not be used. Based on the changing scientific evidence, the plan considers hyaluronan injections in the knee not medically necessary. Use of these injections in all other joints is considered investigational (unproven) because there are so few studies published about other joints. Services that are not medically necessary or investigational are not paid for by the plan.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
### Procedure

<table>
<thead>
<tr>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-articular hyaluronan injections of the knee</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-articular hyaluronan injections, all other joints</td>
<td>Intra-articular hyaluronan injections are considered investigational for all other joints.</td>
</tr>
</tbody>
</table>

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7320</td>
<td>Hyaluronan or derivative, Genvisc 850, for intra-articular injection, 1 mg (new code effective 1/1/17)</td>
</tr>
<tr>
<td>J7321</td>
<td>Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose</td>
</tr>
<tr>
<td>J7322</td>
<td>Hyaluronan or derivative, Hymovis, for intra-articular injection, 1 mg (new code effective 1/1/17)</td>
</tr>
<tr>
<td>J7323</td>
<td>Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose</td>
</tr>
<tr>
<td>J7324</td>
<td>Hyaluronan or derivative, Orthovisc, for intra-articular injection, per dose</td>
</tr>
<tr>
<td>J7325</td>
<td>Hyaluronan or derivative, Synvisc or Synvisc-One, for intra-articular injection, 1 mg</td>
</tr>
<tr>
<td>J7326</td>
<td>Hyaluronan or derivative, Gel-One, for intra-articular injection, per dose</td>
</tr>
<tr>
<td>J7327</td>
<td>Hyaluronan or derivative, Monovisc, for intra-articular injection, per dose</td>
</tr>
<tr>
<td>J7328</td>
<td>Hyaluronan or derivative, for intra-articular injection, 0.1 mg</td>
</tr>
<tr>
<td>Q9980</td>
<td>Hyaluronan or derivative, for intra-articular injection, 1 mg (code terminated effective 1/1/17)</td>
</tr>
</tbody>
</table>

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Evidence Review

Description

Intra-articular (IA) injection of hyaluronan into osteoarthritic joints is proposed to improve pain and 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, and this is the U.S. Food and Drug Administration-approved indication. Other joints (eg, hip, shoulder) are being investigated for IA hyaluronan treatment of osteoarthritis.

Background

Knee osteoarthritis (OA) is common, costly 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 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.

Summary of Evidence

The evidence for intra-articular 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. There are many RCTs 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 IAHA 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 that have estimated 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 and small trial bias. For example, a 2016 meta-analysis found more than a 3-fold larger treatment effect in small trials than in larger trials (ie, >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 that there is a treatment benefit that is clinically significant. The evidence is sufficient to determine qualitatively that the technology is unlikely to improve the net health outcome, thus the treatment is considered not medically necessary.

The evidence for intra-articular 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 did not find statistically significant benefits of the technology on health outcomes, or found benefits that were statistically, but likely not clinically, significant eg, 0.27 points on a 10-point visual analogue scale. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in **Table 1**.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02629380</td>
<td>Early Viscosupplementation After Partial Meniscectomy: a Randomized Controlled Trial (HA-MEN)</td>
<td>90</td>
<td>Mar 2016 (ongoing)</td>
</tr>
<tr>
<td>NCT02280538</td>
<td>Trial to Assess the Structural Effect and Long-term Symptomatic Relief of Intra-articular</td>
<td>300</td>
<td>Jan 2018</td>
</tr>
</tbody>
</table>
### Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

### Practice Guidelines and Position Statements

**American Medical Society for Sport Medicine**

In a 2016 scientific statement from the American Medical Society for Sport Medicine (AMSSM), AMSSM recommended IAHA for “appropriate” patients with knee OA based on high-quality evidence.\(^4\) Patient selection criteria include individuals age 60 and older with Kellgren-Lawrence grade II-III OA. The society also “suggests” IAHA for patients under age 60 with knee OA based on moderate quality indirect evidence.

**American Academy of Orthopaedic Surgeons**

The American Academy of Orthopaedic Surgeons’ (AAOS) 2013 guideline on treatment of OA of the knee states that they cannot recommend using HA for patients with symptomatic knee OA.\(^7\) This is a strong recommendation, meaning that the quality of the supporting evidence is high. This recommendation was based on a meta-analysis of 3 high-strength and 11 moderate-strength studies that showed that the overall effect was less than 0.5 minimally important different units, indicating a low likelihood that an appreciable number of patients achieved
clinically important benefits. AAOS states that practitioners should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present. This replaces a 2008 guideline in which a recommendation could not be made for IAHA due to inconclusive evidence.

The 2009 (reaffirmed 2014) AAOS Clinical Practice Guideline on glenohumeral joint osteoarthritis\(^{33}\) includes a weak grade C recommendation that “the use of injectable viscosupplementation is an option when treating patients with glenohumeral [shoulder] osteoarthritis.” Grade C recommendations are based on poor-quality evidence. In this instance, the recommendation is based on a single case series of 30 patients with OA of the glenohumeral joint who received 3 weekly IA injections of Synvisc\(^{34}\). At 1, 3, and 6 months, clinically significant improvements were seen in pain, function, and quality-of-life measures.

**American College of Rheumatology**

The American College of Rheumatology (ACR) published updated guidelines in 2012 that addressed OA of the hand, hip, and knee.\(^{35}\) A conditional recommendation was given for IAHA to treat OA of the knee. ACR recommends not using IAHA for OA of the hand. For OA of the hip, ACR explicitly makes no recommendation regarding treatment with IAHA.

**Osteoarthritis Research Society International**

The 2014 Osteoarthritis Research Society International guidelines, developed by consensus after review of existing guidelines and systematic reviews, gave an “uncertain” recommendation for the use of intra-articular injection of HA for knee OA and a recommendation of “not appropriate” for multiple-joint OA.\(^{36}\)

**National Institute for Health and Clinical Excellence**

The 2014 guidelines by the National Institute for Health and Clinical Excellence\(^{37}\) state: “Do not offer intra-articular hyaluronan injections for the management of osteoarthritis.”
Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

Several preparations of intra-articular hyaluronan (IAHA) 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); Hylalgan® (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 Hylalgan® (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 Hylalgan® 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®, IAHA 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, eg, 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 3 injections over a 2- to 3-week period. In contrast, 5 weekly injections are recommended for the Hylalgan® and Supartz® products, and 3 to 4 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 3 weekly injections. In 2015, GenVisc® 850 was approved as a course of 3 weekly injections.

In 2000, FDA approved removal of a precautionary statement from the package inserts for Hylalgan 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.
References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/08/12</td>
<td>New policy, add to Medicine section. This policy replaces 5.01.506. Added the table listing FDA approved hyaluronan products and recommended course(s) of treatment per MPC request. The 3rd sentence of the 4th paragraph regarding The product inserts further indicates... was moved from the description to the policy guidelines section for ease of policy administration. Policy approved with 90-day hold for provider notification. The policy effective date is November 7, 2012.</td>
</tr>
<tr>
<td>08/03/12</td>
<td>Correct Error on Related Policy number. Changed from 7.01.118 to 7.01.117.</td>
</tr>
<tr>
<td>08/27/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
</tr>
<tr>
<td>11/07/12</td>
<td>Policy effective after hold for provider notification. 5.01.506 is deleted.</td>
</tr>
<tr>
<td>03/08/13</td>
<td>Policy updated. Rationale and references revised. “in the knee when the above criteria are not met, and” was added to the investigational statement.</td>
</tr>
<tr>
<td>07/16/13</td>
<td>Update Related Policies. Add 7.01.549, and remove 7.01.188 as it was archived.</td>
</tr>
<tr>
<td>11/11/13</td>
<td>Replace Policy. Policy updated with literature review through July 31, 2013; reference 7 added; policy changed to not medically necessary based on new guidelines from the American Academy of Orthopaedic Surgeons. Policy change aligns with UM initiative and recent change in coverage from BCBSA. Policy held for provider notification; the effective date is April 1, 2014.</td>
</tr>
<tr>
<td>12/09/13</td>
<td>Minor update: When this policy was approved last month a sentence was left out. A second policy statement is now included: “Intra-articular hyaluronan injections are considered not medically necessary to treat osteoarthritis of any joint other than the knee.”</td>
</tr>
<tr>
<td>01/23/14</td>
<td>Policy implementation delayed; the effective date of the policy is moved to June 1, 2014.</td>
</tr>
<tr>
<td>03/03/14</td>
<td>Policy implementation delayed; the effective date of the policy is moved to July 1, 2014.</td>
</tr>
<tr>
<td>05/09/14</td>
<td>Revised implementation date September 1, 2014. Delayed due to Plan internal system updates.</td>
</tr>
<tr>
<td>07/24/14</td>
<td>Update Related Policies. Change title to 7.01.549.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>8/25/14</td>
<td>Policy implementation delayed until December 1, 2014.</td>
</tr>
<tr>
<td>12/08/14</td>
<td>Interim review. Policy updated with literature review; the policy statement is unchanged. Intra-articular hyaluronan for osteoarthritis is considered not medically necessary. Effective 03/1/15.</td>
</tr>
<tr>
<td>01/05/15</td>
<td>Coding update. New HCPCS code J7327 added to the policy.</td>
</tr>
<tr>
<td>02/09/15</td>
<td>Policy implementation date extended to May 1, 2015.</td>
</tr>
<tr>
<td>03/13/15</td>
<td>Policy implementation date extended to June 1, 2015.</td>
</tr>
<tr>
<td>03/24/15</td>
<td>Update Related Policies. Change title to 7.01.549.</td>
</tr>
<tr>
<td>04/14/15</td>
<td>Implementation update: Policy will now be effective July 1, 2015. In the interim, see policy 2.01.534 (effective 4/14/15) for coverage (link provided in header).</td>
</tr>
<tr>
<td>06/01/15</td>
<td>Coding update. ICD-9 codes removed; these are not utilized in policy adjudication.</td>
</tr>
<tr>
<td>12/08/15</td>
<td>Annual Review. Policy reviewed with literature search. No change to policy statements.</td>
</tr>
<tr>
<td>01/19/16</td>
<td>Coding update. New HCPCS codes J7328 and Q9980, effective 1/1/16, added to policy.</td>
</tr>
<tr>
<td>09/30/16</td>
<td>Policy moved into new format; no change to policy statements.</td>
</tr>
<tr>
<td>01/01/17</td>
<td>Coding update; added new HCPCS codes J7320 and J7322 effective 1/1/17.</td>
</tr>
</tbody>
</table>

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200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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