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MEDICAL POLICY – 2.01.534

Intra-Articular Hyaluronan Injections for Osteoarthritis

BCBSA Ref. Policy: 2.01.31

Effective Date:	July 1, 2023	RELATED MEDICAL POLICIES:
Last Revised:	June 12, 2023	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

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

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Introduction

Hyaluronan, or sodium hyaluronate, is a natural substance found in some joints of the human body. This substance acts as a lubricant to help the joints work better. There are also other substances similar to hyaluronan that have been used for the past several years to try 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. However, during the past 5 years, re-analysis of the best early medical studies that included thousands of individuals 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. The plan does not pay for services that are not medically necessary or investigational.

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

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

Coding

Code	Description
HCPCS	
J7318	Hyaluronan or derivative, durolane, for intra-articular injection, 1 mg
J7320	Hyaluronan or derivitive, Genvisc 850, for intra-articular injection, 1 mg
J7321	Hyaluronan or derivative, Hyalgan or Supartz, 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
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

Related Information

N/A

Evidence Review

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), the U.S. Food and Drug Administration (FDA) approved indication. Other joints (e.g., hip, shoulder) are being investigated for IA hyaluronan treatment of OA.

Background

Knee Osteoarthritis

Knee 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.

IA injection of hyaluronan has been proposed as a means of restoring the normal viscoelasticity of the synovial fluid in individuals 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.

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. The relevant outcomes are symptoms, functional outcomes, and treatment-related morbidity. Many RCTs have been published over the last 2 decades. While outcomes of these RCTs are 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 that there is no clinically significant benefit; 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 meta-analysis (2016) found more than a 3-fold larger treatment effect in small trials than in larger trials (i.e., more than 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 meaningful. The evidence is insufficient to determine that the technology resultsin an improvement in 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. The 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 that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

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

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05492851	A Double-blind, Randomized Trial Comparing Three Single Dose Injections for Knee Osteoarthritis	165	Aug 2024
Unpublished			
NCT04231318	A Randomized, Double-Blind, Placebo Controlled, Multi-Center Study of a Single Injection Cross-Linked Sodium Hyaluronate Combined With Triamcinolone Hexacetonide (Cingal®) to Provide Symptomatic Relief of Osteoarthritis of the Knee	231	May 2022
NCT04204265[a]	A Prospective Study of a Single Injection Cross-linked Sodium Hyaluronate (MONOVISC) to Provide Symptomatic Relief of Osteoarthritis of Shoulder Joint	25	Mar 2021 (completed)
NCT04204278[a]	A Prospective Study of a Single Injection Cross-linked Sodium Hyaluronate (MONOVISC) to Provide Symptomatic Relief of Osteoarthritis of Ankle Joint	25	Mar 2021 (completed)
NCT04204083[a]	A Prospective Study of a Single Injection Cross-linked Sodium Hyaluronate (MONOVISC) to Provide Symptomatic Relief of Osteoarthritis of Hip Joint	25	Mar 2021 (completed)

NCT: national clinical trial

[a] Denotes industry-sponsored or cosponsored trial

Clinical Input From Physician Specialty Societies and Academic Medical Centers

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

2011 Input

In response to requests, input was received from 5 academic medical centers (6 reviewers) and 3 physician specialty societies while this policy was under review in 2011. Most reviewers agreed that IA hyaluronan of the knee was medically necessary. In addition, those providing input supported an interval of 6 months for repeat injections. In response to a question about total number of treatment courses, there was no consensus.

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a U.S. professional society, an international society with U.S. representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Medical Society for Sport Medicine

In 2016, the scientific statement from the American Medical Society for Sport Medicine recommended IA hyaluronan for "appropriate" patients with knee OA based on high-quality evidence.[14] Patient selection criteria included individuals age 60 and older with Kellgren-Lawrence grade 2 or 3 OA. The society also "suggests" IA hyaluronan for patients under age 60 with knee OA based on moderate-quality indirect evidence.

American Academy of Orthopaedic Surgeons

In 2021, the guidelines from the American Academy of Orthopaedic Surgeons (AAOS) on treatment of osteoarthritis of the knee indicated that AAOS does not recommend routine use of intra-articular hyaluronic acid for patients with symptomatic knee osteoarthritis.[47] This recommendation was moderate. It was based on a meta-analysis of 28 studies that showed 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. These guidelines replaced 2013 guidelines, which included a strong recommendation against use of intra-articular hyaluronic acid.

In 2017, the AAOS clinical practice guidelines on hip OA included a recommendation that IA hyaluronic acid could not be recommended in patients with symptomatic hip OA, because it was not better than placebo.[48] This was based on strong evidence as assessed in 8 high-quality studies that evaluated IA hyaluronan against corticosteroids and placebo. Several studies showed no difference in patient pain and function after treatment with IA hyaluronan against placebo. Studies reviewing different formulations of IA hyaluronan were also considered.

In 2009 (reaffirmed in 2014), the AAOS clinical practice guidelines on glenohumeral joint OA included a weak grade C recommendation that the "use of injectable viscosupplementation is an option when treating patients with glenohumeral [shoulder] osteoarthritis."[49] Grade C recommendations are based on poor-quality evidence. In this instance, the recommendation was based on a single case series of 30 patients with OA of the glenohumeral joint who received 3 weekly IA injections of hylan G-F 20 (Synvisc).[50] At 1, 3, and 6 months, clinically significant improvements were seen in pain, function, and quality of life measures. In 2020, the updated AAOS clinical practice guidelines stated that "strong evidence supports that there is no benefit in the use of hyaluronic acid in the treatment of glenohumeral joint osteoarthritis."[51]

American College of Rheumatology

In 2019, the American College of Rheumatology updated is guidelines on OA of the hand, hip, and knee.[52] A conditional recommendation against the use of intra-articular hyaluronic acid was given for the treatment of OA of the knee and first carpometacarpal joint of the hand. The College also made a strong recommendation against the use of intra-articular hyaluronic acid for the treatment of osteoarthritis of the hip. These recommendations were informed by a review indicating that the effect size of hyaluronic acid injections compared to saline injections approaches 0 when analysis is limited to trials with low risk of bias. While the evidence of lack of benefit is higher quality for the hip, the conditional recommendation for osteoarthritis of the knee and hand was made in the context of clinical shared decision-making that recognizes the treatment may provide benefit when alternatives have failed to provide benefit and have been exhausted.

Osteoarthritis Research Society International

In 2014, the Osteoarthritis Research Society International (OARSI) guidelines, developed by consensus after review of existing guidelines and systematic reviews, gave an "uncertain" recommendation for the use of IA hyaluronan for knee OA and a recommendation of "not appropriate" for multi-joint OA.[53]

In 2019, OARSI updated these guidelines, as derived from expert consensus and review of high-quality meta-analytic data. Intra-articular hyaluronic acid was conditionally recommended for the treatment of knee osteoarthritis for longer term treatment effect, as it was associated with symptom improvement beyond 12 weeks with a favorable safety profile. This recommendation was provided with high consensus for patients with comorbidities (e.g., gastrointestinal, cardiovascular, frailty). This recommendation was provided with low consensus for patients with no comorbidities. The use of hyaluronic acid for the treatment of hip or polyarticular osteoarthritis was not recommended.[54]

National Institute for Health and Clinical Excellence

In 2022, the clinical guideline issued by the National Institute for Health and Care Excellence for osteoarthritis diagnosis and management stated: "Do not offer intra-articular hyaluronan injections to manage osteoarthritis."[55]

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

Several preparations of intra-articular (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® (Sanofi)
- GenVisc 850® (OrthogenRX)
- Gel-One® (Zimmer Biomet)

- Hyalgan® (Fidia Pharma)
- Supartz FX® (Bioventus)
- Orthovisc® (Anika)
- Euflexxa®, previously named Nuflexxa (Ferring)
- Monovisc® (Anika Therapeutics)
- Durolane® (Bioventus)
- GELSYN-3™ (Bioventus)
- Synojoynt™ (Arthrex)
- Hymovis® (Fidia Pharma)
- TriVisc® (OrthogenRX)
- Visco-3™ (Zimmer Biomet)
- Triluron® (Fidia Pharma)

Most products are manufactured from rooster combs, except for Durolane®, Euflexxa®, Orthovisc®, Monovisc®, Gel-Syn™, Hymovis®, TriVisc®, and GenVisc® 850, which are produced from bacterial fermentation. Also, Synvisc® and other products undergo 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 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 3 injections over a 2- to 3-week period. In contrast, 5 weekly injections are recommended for the Hyalgan® and Supartz™ products, and 3 to 4 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 GELSYN-3™ was approved as a course of 3 weekly injections. In 2015, GenVisc 850® was approved as a course of 3 weekly injections and Hymovis® as a series of 2 injections one week apart. In 2017, Durolane was approved as a single-dose treatment and TriVisc® as a course of 3 weekly injections. In 2018, Synojoynt™ and Visco-3™ were approved as a course of 3 weekly injections. In 2019, Triluron™ was approved as a course of 3 weekly injections.

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

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

FDA product code: MOZ

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History

Date	Comments
05/08/12	New policy, add to Medicine section. This policy replaces 5.01.506. Added the table listing FDA approved hyaluranon 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.
08/03/12	Correct Error on Related Policy number. Changed from 7.01.118 to 7.01.117.
08/27/12	Update Coding Section – ICD-10 codes are now effective 10/01/2014.
11/07/12	Policy effective after hold for provider notification. 5.01.506 is deleted.

Date	Comments
03/08/13	Policy updated. Rationale and references revised. "in the knee when the above criteria are not met, and" was added to the investigational statement.
07/16/13	Update Related Policies. Add 7.01.549, and remove 7.01.188 as it was archived.
11/11/13	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.
12/09/13	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."
01/23/14	Policy implementation delayed; the effective date of the policy is moved to June 1, 2014.
03/03/14	Policy implementation delayed; the effective date of the policy is moved to July 1, 2014.
05/09/14	Revised implementation date September 1, 2014. Delayed due to Plan internal system updates.
07/24/14	Update Related Policies. Change title to 7.01.549.
08/25/14	Policy implementation delayed until December 1, 2014.
12/08/14	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.
01/05/15	Coding update. New HCPCS code J7327 added to the policy.
02/09/15	Policy implementation date extended to May 1, 2015.
03/13/15	Policy implementation date extended to June 1, 2015.
03/24/15	Update Related Policies. Change title to 7.01.549.
04/14/15	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).
06/01/15	Coding update. ICD-9 codes removed; these are not utilized in policy adjudication.
12/08/15	Annual Review. Policy reviewed with literature search. No change to policy statements.
01/19/16	Coding update. New HCPCS codes J7328 and Q9980, effective 1/1/16, added to policy.
07/01/16	Annual Review, approved June 14, 2016. Policy updated with literature review through February 12, 2016; references 10-18, and 21-24 added. Policy statements unchanged. Introduction added. Background information deleted.

Date	Comments
09/30/16	Policy moved into new format; no change to policy statements.
01/01/17	Coding update; added new HCPCS codes J7320 and J7322 effective 1/1/17.
07/01/17	Annual Review, approved June 6, 2017. Policy updated with literature review through February 23, 2017; references 5, 11, 20-22, and 29 added. Policy statements unchanged.
01/01/18	Removed HCPCS code Q9980 as it terminated on 1/1/17.
07/01/18	Annual Review, approved June 5, 2018. Policy updated with literature review through February 2018; references 29 and 33 added. Policy statements unchanged.
01/01/19	Coding update, added new HCPCS codes J7318 and J7329 (new codes effective 1/1/19)
07/01/19	Annual Review, approved June 4, 2019. Policy updated with literature review through February 2019; reference added. Policy statements unchanged.
10/01/19	Coding updated, added HCPCS J7331 and J7332 (new codes effective 10/1/19).
07/01/20	Annual Review, approved June 4, 2020. Policy updated with literature review through January 2020; references added. Policy statements unchanged. HCPCS code J7333 removed.
07/02/20	Coding update. Removed HCPCS codes J7331 and J7332. Related policy 7.01.549 removed.
12/01/20	Coding update. Added HCPCS codes J7331, J7332, J7333.
04/01/21	Coding update. Added term date to HCPC J7333.
07/01/21	Annual Review, approved June 1, 2021. Policy updated with literature review through January 11, 2021; references added. Policy statements unchanged.
07/01/22	Policy renumbered from 2.01.31 Intra-Articular Hyaluronan Injections for Osteoarthritis to 2.01.534 Intra-Articular Hyaluronan Injections for Osteoarthritis, approved June 14, 2022. Policy updated with literature review through February 28, 2022; reference added. Policy statement unchanged. Removed HCPCS code J7333.
07/01/23	Annual Review, approved June 12, 2023. Policy updated with literature review through February 13, 2023; reference added. Policy statements unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

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Washington residents: You can also file a civil rights complaint with the Washington State Office of the Insurance Commissioner, electronically through the Office of the Insurance Commissioner Complaint Portal available at https://www.insurance.wa.gov/file-complaint-or-check-your-complaint-status, or by phone at 800-562-6900, 360-586-0241 (TDD). Complaint forms are available at https://fortress.wa.gov/oic/onlineservices/cc/pub/complaintinformation.aspx.

Alaska residents: Contact the Alaska Division of Insurance via email at insurance@alaska.gov, or by phone at 907-269-7900 or 1-800-INSURAK (in-state, outside Anchorage).

Language Assistance

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 800-722-1471 (TTY: 711).

PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 800-722-1471 (TTY: 711).

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CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 800-722-1471 (TTY: 711).

주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 800-722-1471 (TTY: 711) 번으로 전화해 주십시오.

ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 800-722-1471 (телетайп: 711).

LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 800-722-1471 (TTY: 711).

MO LOU SILAFIA: Afai e te tautala Gagana fa'a Sāmoa, o loo iai auaunaga fesoasoan, e fai fua e leai se totogi, mo oe, Telefoni mai: 800-722-1471 (TTY: 711).

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ማስታወሻ: የሚናገሩት ቋንቋ ኣማርኛ ከሆነ የትርጉም እርዳታ ድርጅቶች፣ በነጻ ሊያግዝዎት ተዘጋጀተዋል፡ ወደ ሚከተለው ቁጥር ይደውሉ 800-722-1471 (መስማት ለተሳናቸው፡ 711).

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เรียน: ถ้าคุณพูดภาษาไทยคุณสามารถใช้บริการช่วยเหลือทางภาษาได้ฟรี โทร 800-722-1471 (TTY: 711).

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