Monovisc (hyaluronate sodium, stabilized)

STRENGTH	DOSAGE FORM	ROUTE	GPID
88 mg/4 mL	pre-filled syringe	intraarticular	36397

MANUFACTURER
Anika Therapeutics, Inc.

INDICATION(S)

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

DRUG CLASS

INFLAMMATORY DISEASE; ANTI-INFLAMMATORY/ANTIARTHRITICS AGENTS, MISC.

PLACE IN THERAPY
Monovisc joins Synvisc-One and Gel-One as a single-injection hyaluronate (HA) preparation and is the 8th FDA-approved viscosupplement for use in OA of the knee. Monovisc has a high molecular weight (between 1 and 2.9 million Dalton) and is composed of partially cross-linked sodium hyaluronate. This formulation is designed to deliver a comparable HA dose to three injections of Orthovisc, Anika's other viscosupplement. The other agents available in this class require multiple injections per treatment: Synvisc (3 injections), Supartz (5 injections), Orthovisc (3-4 injections), Euflexxa (3 injections), and Hyalgan (5 injections).

In general, guidelines focused on the treatment of OA in the knee recommend starting with nonpharmacological therapy such as weight loss/management, physical exercise including land-based and water-based therapies, strength training, and education. The pharmacological algorithm begins with non-opioid analgesics (e.g. acetaminophen), followed by topical and oral non-steroidal anti-inflammatory drugs (NSAIDs) while duloxetine and tramadol remain an option if NSAIDs are ineffective or contraindicated. In patients with an inadequate response or a contraindication to these therapies, intra-articular injections of corticosteroids or HA may be considered.

Due to the questionable clinical significance of trials showing positive effects on pain and function, the use of HA is not currently recommended or is designated inconclusive in recommendations by practice guidelines, including the American Academy of Orthopaedic Surgeons, the Osteoarthritis Research Society International, and the National Institute of Health and Clinical Excellence. There is a lack of reliable evidence to demonstrate the superiority of one HA product over another.

Single injection Monovisc could possibly reduce any additional medical expenditure related to administration costs and decrease the number of physician visits required, thus possibly favoring it over multiple injection products. Compared to Synvisc-One and Gel-One, the only evident safety or efficacy advantage is that Monovisc is derived from bacterial fermentation (*Streptococcus equi*) instead of chicken combs (a contraindication to those allergic to avian proteins, feathers, or egg products).

EFFICACY

The efficacy of Monovisc was established in a randomized, placebo-controlled, double-blind, multicenter study that included 369 patients with symptomatic primary OA of the knee. Inclusion criteria consisted of patients aged 35-75, baseline index knee Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Score between 200 and 400 mm, baseline contralateral knee WOMAC Pain Score <150 mm, and wash-out of all NSAIDs, corticosteroids, and other analgesics prior to study start. The primary efficacy endpoint was the proportion of Monovisc-treated patients achieving ≥ 40% relative improvement and ≥ 15mm absolute improvement from baseline in WOMAC Pain Score versus placebo (saline)-treated patients through 12 weeks. Monovisc did not demonstrate superiority over saline injections for the primary endpoint (P=0.145).

Based on the findings of the above trial and request from the FDA for a new data analysis, the manufacturer submitted a non-inferiority analysis comparing an equivalent Monovisc dose with Orthovisc (a single dose of Monovisc is equivalent to 3 doses of Orthovisc). The data for Orthovisc came from previously submitted clinical trial efficacy data. The patient and baseline demographics data from the Monovisc efficacy trial was determined to be similar to the populations of the Orthovisc studies. The primary efficacy endpoints for non-inferiority were the proportion of patients achieving a 20%, 40%, and 50% improvement in baseline in WOMAC Pain Score through weeks 21-22. The results from the primary endpoint analysis show that Monovisc is non-inferior to 3 injections of Orthovisc across all thresholds.

Table 9. Mean Proportion of Responders from GEE Model (Weeks 7-22)

Variable	M1 PP N=164 %, CI	M1 ITT N=181 %, CI	O3A1 N= 90 %, CI	O3 N= 83 %, CI	O3A1/O3 N=173 %, CI	O4 N= 104 %, CI	A4 N=100 %, CI	Saline N= 81 %, CI
20% Improvement in WOMAC	**74.2** (67.7, 80.7)	**72.4** (65.8,79.1)	**63.0** (52.8, 73.2)	**70.8** (60.8, 80.8)	**67.0** (52.8, 81.3)	**73.1** (64.4, 81.8)	**62.9** (53.7, 72.2)	**60.2** (49.3, 71.1)
40% Improvement in WOMAC	**61.8** (54.5, 69.0)	**58.9** (51.6, 66.2)	**50.2** (39.6, 60.7)	**54.5** (43.5, 65.4)	**52.5** (37.3, 67.7)	**63.4** (54.0, 72.9)	**48.0** (38.4, 57.6)	**41.0** (30.1, 52.0)
50% Improvement in WOMAC	**53.6** (46.2, 61.0)	**51.2** (43.8, 58.6)	**43.3** (32.9, 53.8)	**46.3** (35.4, 57.3)	**45.0** (29.9, 60.1)	**55.6** (45.9, 65.4)	**42.6** (33.2, 52.1)	**34.4** (23.8, 44.9)

M1= 1 injection of Monovisc; 03A1= 3 injections of Orthovisc + 1 arthrocentesis; O3= 3 injections of Orthovisc; O4= 4 injections of Orthovisc; A4= 4 arthrocentesis procedures; Saline= 3 injections of saline

SAFETY

Monovisc is contraindicated in patients with known hypersensitivity to hyaluronate preparations, gram-positive bacterial proteins, or known systemic bleeding disorders. Monovisc should not be injected in the knees of patients with infections or skin diseases in the area of the injection site or joint.

The most common adverse reactions observed with Monovisc were arthralgia (3.8%), injection site pain (1.6%), and joint swelling (1.1%). Adverse events related to treatment were considered typical of viscosupplementation injections. There were no serious adverse events related to Monovisc.

DOSAGE

Monovisc is injected into the knee joint and is administered as a single intra-articular injection. Strict aseptic administration technique by healthcare professionals must be followed.

COST

Drug	Cost/unit	Cost per treatment
Monovisc (hyaluronate sodium, stabilized) 88mg syringe	AWP=$1170	$1170
Orthovisc (hyaluronate sodium) 15mg syringe	AWP=$384	$1536
Synvisc (hylan G-F 20) 16mg syringe	AWP=$398	$1195
Synvisc-One (hylan G-F 20) 48mg syringe	AWP=$1195	$1195
Gel-One (hyaluronate sodium, cross-linked) 30mg syringe	AWP=$1170	$1170
Supartz (hyaluronate sodium) 25mg syringe	AWP=$242	$1209
EuFlexxa (hyaluronate sodium) 20mg syringe	AWP=$370	$1110
Hyalgan (hyaluronate sodium) 20mg syringe	AWP=$198	$990

FORMULARY PLACEMENT RECOMMENDATIONS

Based on this initial assessment of available clinical and financial information, consider NOT ADDING Monovisc to the formulary pending complete review by the appropriate oversight committee for the plan.

REFERENCES

Monovisc [Prescribing Information]. Bedford, MA: Zogenix; December 2013.

American Academy of Orthopaedic Surgeons (AAOS). Treatment of Osteoarthritis of the Knee. Evidence-Based Guideline. 2nd Edition. May 18, 2013.

National Institute for Health and Care Excellence (NICE). Osteoarthritis: national clinical guideline for care and management in adults. Developed by the National Collaborating Centre for Chronic Conditions. London, UK: Royal College of Physicians; 2008.

McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014 Mar;22(3):363-88.

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.