DRUG NEWS

Viscosupplementation: What is the evidence for hyaluronic acid intra-articular injections?

BOTTOM LINE: There is a lack of quality evidence to support or refute the use of HA intra-articular injections in the treatment of osteoarthritis. While most organizations do not recommend the routine use of injectable hyaluronic acid, it is an option for patients not obtaining relief from first line therapies. Similarly there is insufficient evidence on the safety and efficacy differences among products to support the use of a particular molecular weight formulation or a particular hyaluronic acid product. There is however, evidence to suggest that the number of hyaluronic acid injections impacts potential efficacy and safety with 2-4 weekly injections being superior to single injection or 5+ injections[20]. Selection of an appropriate product should be based on individual patient characteristics and needs. (See Comparison Chart below)

Classification of hyaluronic acid:

- Hyaluronic acid is a polysaccharide consisting of repeating molecules of β-D-glucuronic acid and β-D-*N*-acetylglucosamine, with molecular mass ranging from 6500 to 10,900kDa[1]. Hyaluronate occurs naturally in cartilage and synovial fluid[2]. Injectable hyaluronic acid products are derived from avian sources (rooster combs) or bacterial fermentation.

Use/Place in Therapy:

- Hyaluronate intra-articular injection is used to provide intra-articular lubrication and may have anti-inflammatory, analgesic and chondroprotective effects on articular cartilage and joint synovium[1,2].
- All products are SK non-formulary
- NIHB provides exception listing status for the following criteria: OA of the knee when other treatments failed. Other joints not considered for approval[21].

Indication:

- Conditionally recommended by American College of Rheumatology (ACR) in cases of mild to moderate OA, in those who experience inadequate pain relief with first-line therapies[4].
- Osteoarthritis Research Society International (OARSI), the American Academy of Orthopaedic Surgeons (AAOS), and the National Institute for Health and Care Excellence (NICE) do not recommend hyaluronic acid injections for osteoarthritis due to uncertain appropriateness and lack of evidence supporting use [8,9,22].

Drug Interactions (DI)[5]:

- No DI's found with drugs, food, tobacco, ethanol

Adverse Events (AE)[5]:

Adverse events are primarily mild and of short duration with the most common including:

- arthralgia[12.6%]
- injection site pain[2.5%]
- injection site reaction[0.2%]

Administration:

- for intra-articular injection only
- hyaluronan can precipitate in the presence of quaternary ammonium salts (ie benzalkonium)
- do not inject if presence of skin/joint infection or effusion at injection site
- optimal safety and efficacy suggested to result from 2-4 weekly injections with a single injection being less efficacious and 5+ injections increasing the risk of adverse events without a corresponding increase in potential efficacy[20]

Warnings/Contraindication (CI)[5,6, 7,]:

- contraindicated if hypersensitivity to hyaluronate or any component of formulation
- preparations containing avian sources may increase risk of immunogenicity
- knee/joint infections
- history of anaphylaxis
- hypersensitivity to gram positive bacterial proteins
- safety not studied in pregnancy/lactation/children
- Hylan G-F 20 preparation (Synvisc®) – cases of acute calcium pyrophosphate crystal arthritis (pseudogout) have occurred two or three days after hyaluronate injection [7]
- Monovisc CI if systemic bleeding disorders[11]

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Viscosupplementation: Hyaluronic Acid Intra-articular Injections Comparison Chart

Trade name	Drug	Indication	Dose	Cost (wholesale)	Comments
Neovisc[10]	Sodium hyaluronate	OA Knee	-Single (60mg/2ml) -Multi (20mg/2ml)* *3-5 injections	$376 (6ml) $300 (2mlx3)	Linear High MW* Non-avian
Monovisc[11]	Sodium hyaluronate	OA Knee	-80mg/4ml	$335 (4ml)	Cross linked High MW Non-avian CI if systemic bleeding disorders
Cingal[12]	Hyaluronic acid/ triamcinolone hexacetonide	OA Knee	-88mgHA+ 18mgTH/4ml	$415 (4ml)	Cross-linked High MW non-avian
Orthovisc[13,14]	Sodium hyaluronate	OA Knee	Depends upon joint space. Max 30mg/2ml for knee (1 injection weekly for 3 weeks)	$323 (2mlx3)	Linear High MW Avian
Synvisc[14,15] **Synvisc-One**[16]	Hylan-G-F20	OA Knee, Hip, Ankle, Shoulder	Knee OA -16mg/2ml (1 injection weekly for 3 weeks‡) Hip, ankle, shoulder -16mg/2ml single injection (2nd injection in 1-3 months if inadequate relief) Synvisc-one -48mg/6ml single injection	$136 (2ml) $407 (2mlx3) $414 (6ml)	Mix of cross-linked and linear High MW Avian Contains hylan A&B CI if venous or lymphatic stasis ‡MAX 6 injections in 6 months with 4 weeks in between treatment regimens)
Durolane[1,7,18]	1% Hyaluronic acid	OA knee, hip, ankle, fingers, toes. Post arthroscopy pain (within 3 months) if OA present	-20mg/1ml suitable for finger/toes -1-2ml *ankle -60mg/3ml *hip, knee, ankle	$150 (1ml) $405 (3ml)	High MW Non-avian Re-injections may occur every 6 months (not studied with shorter interval)
Euflexxa[19]	Sodium hyaluronate	OA Knee	-20mg/2ml (1 injection weekly for 3 weeks)	$341 (2mlx3)	Linear High MW Non-avian Safety of repeat cycles established up to a year
Suplasyn	Manufacturer uncertain that this product existed.	Unable to provide a product monograph or package insert.	NA	NA	NA

*molecular weight

use in various joints | contains glucocorticoid | produced from avian sources | unique contraindicatons

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