

SPECIFICATION: SPC-000121

Title: DUROLANE® US Claims Book

Nondisclosure Statement

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1. INTRODUCTION

The purpose of the DUROLANE Claims Book is to provide all pertinent information for the DUROLANE brand to assist in developing, reviewing and approving DUROLANE marketing materials. This Product and Brand Book contains approved messaging, supported claims with references, plus branding and writing information. The expectation is that promotional materials will use the exact wording contained within the Claims Book. Deviation from approved wording will result in approval delays.

2. SCOPE

The specifications in this DUROLANE Product and Brand Book apply only to DUROLANE materials for US audiences. DUROLANE is marketed by Bioventus LLC and is available by prescription for use in the United States. All promotional material requires a unique identifier (generated from the Document Management System), together with a revision level and date.

3. STANDARDS AND PROCEDURES

3.1. External Standards and Regulations

Reference	Description
Section 502 of the FD&C Act	Misbranded drugs and devices
Federal Trade Commission Act (FTC Act), (15 U.S.C. § 52-55)	Prohibits the dissemination of misleading claims for food, drugs, devices, services, or cosmetics
Part 820.120 of the Code of Federal Regulations (CFR), Title 21	Medical devices: Device labeling

3.2. Internal Procedures and Documents

Reference	Description
Q105007-BC	Legal, Medical, and Regulatory (LMR) Approval Process
0059335	Dissemination of Promotional Material

4. DEFINITIONS

N/A.

5. ABBREVIATIONS

AE	Adverse events
CI	Confidence Interval
HA	Hyaluronic acid
IA	Intra-articular
IFU	Instructions for Use
MPA	Methylprednisolone acetate
NASHA	Non-animal, stabilized hyaluronic acid
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
TKR	Total knee replacement
TRAE	Treatment-related adverse event

6. INSTRUCTIONS

DUROLANE Indications Statements - Country-specific indication statement must be on all customer-facing materials. For materials intended for use in multiple countries, it must be clear which countries have which indications.

Consult the IFU document associated with the territory of distribution to verify the following information for DUROLANE in that area:

- The specific size available (i.e. 3 mL)
- The exact wording for the registered indication
- The precise claims that can be made

ATTENTION:

Claims followed by ‡ require indication/reference adjustment based on region.

Claims must be used with the associated graph when present and used as a whole.

Whenever the following reference is used to support a claim, a disclaimer must be added stating that this study does not contain data specific to DUROLANE. This is also indicated throughout the document with an asterisk (*).

- Altman R, Lim S, Steen RG, Dasa V. Hyaluronic acid injections are associated with delay of total knee replacement surgery in patients with knee osteoarthritis: evidence from a large U.S. health claims database. *PLoS One*. 2015;10(12):e0145776. doi:10.1371/journal.pone.0145776

6.1. DUROLANE US Indication of Use

Claim	Summary of Indication for Use: DUROLANE is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacological therapy or simple analgesics, e.g. acetaminophen.  Do not inject DUROLANE in patients with knee joint infections, skin diseases, or other infections in the area of the injection site. Do not administer to patients with known hypersensitivity or allergy to sodium hyaluronate preparations. Risks can include transient pain or swelling at the injection site. DUROLANE has not been tested in pregnant or lactating women, or children. Full prescribing information can be found in product labeling, at www.DUROLANE.com, or by contacting Bioventus Customer Service at 1-800- 836-4080.
Reference	DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019.

7. DUROLANE General Market Claims

These claims are general statements that are supported by published evidence. They do not include value statements.

7.1. Messaging for Physicians

These claims provide information about OA and DUROLANE specifically for physicians, and address questions that physicians may have.

Claim	• Pain relief is a key priority for patients with OA.¹ • Knee OA patients cite duration of pain relief as their most important treatment outcome.² • Most knee OA patients hope to restore daily activities such as walking up and down stairs.² • Most patients are motivated to find effective treatments to help them walk up and down stairs.²
Reference	1. Papandony MC, Chou L, Seneviwickrama M, et al. Patients' perceived health service needs for osteoarthritis (OA) care: a scoping systematic review. <i>Osteoarthritis Cartilage</i>. 2017;25(7):1010-25. doi:10.1016/j.joca.2017.02.799 2. Bioventus LLC. Knee OA patient market research report. Data on file, RPT-001416[A]. August 2021.

Claim	Powerful and long-lasting pain relief¹⁻⁴ NOTE: One or all references can be used to support this claim; do not need all references every time.
Reference	1. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019. 2. Leighton R, Åkermark C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009 3. McGrath AF, McGrath AM, Jessop ZM, et al. A comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. <i>J Arthritis</i>. 2013;2(1):1000108. doi:10.4172/2167-7921.1000108 4. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther</i>. 2015;17(1):51. doi:10.1186/s13075-015-0557-x

Claim	Long lasting by design¹⁻³ NOTE: All references should be used to support this claim.
Reference	1. Ågerup B, Berg P, Åkermark C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. <i>BioDrugs</i>. 2005;19(1):23-30. doi:10.2165/00063030-200519010-00003 2. Edsman K, Hjelm R, Lärkner H, et al. Intra-articular duration of Durolane™ after single injection into the rabbit knee. <i>Cartilage</i>. 2011;2(4):384-8. doi:10.1177/1947603511400184 3. Lindqvist U, Tolmachev V, Kairemo K, Åström G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. <i>Clin Pharmacokinet</i>. 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004

Claim	- The DUROLANE power of one^{1,2} - The DUROLANE difference^{3,4} - Choose the power of one^{1,2} - All the convenience of a single injection. Powerful pain relief.¹⁻⁵ - Deliver relief that lasts. Choose convenience without compromise in a single injection.¹⁻⁵ - The power of one for lasting pain relief.¹⁻⁵ - One injection is all you need for powerful pain relief that lasts.¹⁻⁵ NOTE: For claims using all three references (Leighton, McGrath, and Zhang) - one or all three references can be used to support the claims; do not need all three references every time.
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Reference	1. Ågerup B, Berg P, Åkermark C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. <i>BioDrugs</i>. 2005;19(1):23-30. doi:10.2165/00063030-200519010-00003 2. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019. 3. McGrath AF, McGrath AM, Jessop ZM, et al. A comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. <i>J Arthritis</i>. 2013;2(1):1000108. doi:10.4172/2167-7921.1000108 4. Leighton R, Åkermark C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009 5. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther</i>. 2015;17(1):51. doi:10.1186/s13075-015-0557-x
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7.2. Messaging for Patients

These claims provide information about OA and DUROLANE specifically for patients, and address questions that patients may have.

Claim (Patient)	• Are you looking for powerful and long-lasting pain relief from knee osteoarthritis?¹⁻⁵ • Ask your doctor about DUROLANE, or visit www.durolane.com. • DUROLANE is a powerful and lasting HA, which is injected directly into the joint.¹⁻⁵ • Choose convenience without compromise and get comparable results.⁵ • Choose convenience without compromise.⁵ NOTE: For claims using all three references (Leighton, McGrath, and Zhang) - one or all three references can be used to support the claims; do not need all three references every time.
Reference	1. Ågerup B, Berg P, Åkermark C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. <i>BioDrugs</i>. 2005;19(1):23-30. doi:10.2165/00063030-200519010-00003 2. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019. 3. McGrath AF, McGrath AM, Jessop ZM, et al. A comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. <i>J Arthritis</i>. 2013;2(1):1000108. doi:10.4172/2167-7921.1000108 4. Leighton R, Åkermark C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009 5. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a

	multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther.</i> 2015;17(1):51. doi:10.1186/s13075-015-0557-x
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Claim (Patient)	- How do I know if I have OA? - Only a doctor can diagnose you, but there are four important warning signs that mean you should talk to your provider:¹ - Pain – The pain may be constant or it may come and go. Pain may occur while at rest or while moving. - Swelling – Sometimes arthritis causes the skin over the affected joint to become swollen, red, and warm to the touch. If the swelling lasts longer than two days, or flares up more than three times a month, you should visit your doctor. - Stiffness - Stiffness is commonly experienced with arthritis upon waking in the morning or after prolonged sitting. If morning stiffness lasts longer than an hour, arthritis may be suspected. - Difficulty moving a joint – Difficulty or pain when moving the affected joint. - If any of the above statements apply to you, you should see a doctor. Getting an accurate diagnosis is a key step to receiving appropriate treatment.¹
Reference	Arthritis Foundation. Do I have arthritis? www.arthritis.org/health-wellness/about-arthritis/understanding-arthritis/do-i-have-arthritis. Accessed June 24, 2022.

Claim (Patient)	- What is osteoarthritis (OA)? - OA is often referred to as “degenerative joint disease,” which usually develops slowly over time. Gradually, cartilage on the surface of the joint starts to get damaged and wears away. This leads to pain and stiffness in the joint.¹ - What is hyaluronic acid (HA)? - HA is a sugar molecule, called a polysaccharide, found naturally throughout the human body. It is an important component of synovial fluid (joint fluid). The synovial fluid allows joints to move easily and freely while also absorbing the shock of daily activity. In a healthy joint, HA helps to protect bones and other joint tissues from injury and disease.²⁻³
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Graphic (Patient)	Inside an OA Joint Normal Joint OA Joint 1. Normal cartilage: Provides a smooth surface, allowing bones to move easily across each other^{3,4} 2. Synovial fluid: Lubricates and provides shock absorption during activity due to a high concentration of HA^{3,5} 3. Normal bone: Provides strength and support for the body's tissues⁶ 4. Eroded cartilage: If completely worn away, bones may scrape painfully against each other¹ 5. OA synovial fluid: The osteoarthritis disease leads to reduced production of HA, of poor quality^{5,7} 6. OA bone: Bony spur growths (osteophytes)⁵
Reference	1. Hsu H, Siwiec RM. Knee osteoarthritis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 25, 2021. 2. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019. 3. Tamer TM. Hyaluronan and synovial joint: function, distribution and healing. <i>Interdiscip Toxicol</i>. 2013;6(3):111-25. doi:10.2478/intox-2013-0019 4. Roughley PJ, Mort JS. The role of aggrecan in normal and osteoarthritic cartilage. <i>J Exp Orthop</i>. 2014;1(1):8. doi:10.1186/s40634-014-0008-7 5. Mora JC, Przkora R, Cruz-Almeida Y. Knee osteoarthritis: pathophysiology and current treatment modalities. <i>J Pain Res</i>. 2018;11:2189-96. doi:10.2147/JPR.S154002 6. Clarke B. Normal bone anatomy and physiology. <i>Clin J Am Soc Nephrol</i>. 2008;3(suppl 3):S131-9. doi:10.2215/CJN.04151206 7. Li H, Guo H, Lei C, et al. Nanotherapy in joints: increasing endogenous hyaluronan production by delivering hyaluronan synthase 2. <i>Adv Mater</i>. 2019;31(46):e1904535. doi:10.1002/adma.201904535

Claim (Patient)	- HA in your joints is continuously broken down and replaced over time.¹ - When you have OA, HA becomes diluted and breaks down faster.^{1,2} This is associated with increased inflammatory processes that can degrade the cartilage in your knee.^{3,6} - The pain caused by inflammation limits movement,^{3,4} which in turn can lead to further deterioration of the joint.⁵
Reference	- Li H, Guo H, Lei C, et al. Nanotherapy in joints: increasing endogenous hyaluronan production by delivering hyaluronan synthase 2. <i>Adv Mater.</i> 2019;31(46):e1904535. doi:10.1002/adma.201904535 - Mora JC, Przkora R, Cruz-Almeida Y. Knee osteoarthritis: pathophysiology and current treatment modalities. <i>J Pain Res.</i> 2018;11:2189-96. doi:10.2147/JPR.S154002 - Altman RD, Manjoo A, Fierlinger A, Niazi F, Nicholls M. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. <i>BMC Musculoskelet Disord.</i> 2015;16:321. doi:10.1186/s12891-015-0775-z - Mease PJ, Hanna S, Frakes EP, Altman RD. Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. <i>J Rheumatol.</i> 2011;38(8):1546-51. doi:10.3899/jrheum.100759 - Brody LT. Knee osteoarthritis: clinical connections to articular cartilage structure and function. <i>Phys Ther Sport.</i> 2015;16(4):301-16. doi:10.1016/j.ptsp.2014.12.001 - DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019.

8. OA/HA Class Related Claims

These claims describe OA and the role of HA.

Claim	- HA treatment in patients with knee OA is associated with a delay in a TKR.^{1,2*} - Patients who received ≥ 5 courses of HA delayed TKR by 3.6 years.^{1*} - A retrospective analysis of 50,349 US patients has shown that HA injections increase time to TKR in a treatment course-dependent manner.^{1*} - Injections of supplemental HA can help delay the need for knee replacement surgery.^{1*} - Repeated injections of HA therapy can delay the need for knee replacement surgery.^{1*} *The study by Altman et al. 2015 does not contain data specific to DUROLANE.
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Graphic [Altman 2015: 6a/Table3]	 <table border="1"> <thead> <tr> <th>Treatment Group</th> <th>Time to TKR (median days)</th> </tr> </thead> <tbody> <tr> <td>Time to TKR without HA Treatment</td> <td>114 Days</td> </tr> <tr> <td>HA Course 1</td> <td>386 Days</td> </tr> <tr> <td>HA Course 2</td> <td>648 Days</td> </tr> <tr> <td>HA Course 3</td> <td>875 Days</td> </tr> <tr> <td>HA Course 4</td> <td>1054 Days</td> </tr> <tr> <td>HA Course ≥5</td> <td>1312 Days</td> </tr> </tbody> </table> (all versus no HA, $p < 0.0001$) Time to TKR (median days)	Treatment Group	Time to TKR (median days)	Time to TKR without HA Treatment	114 Days	HA Course 1	386 Days	HA Course 2	648 Days	HA Course 3	875 Days	HA Course 4	1054 Days	HA Course ≥5	1312 Days
Treatment Group	Time to TKR (median days)														
Time to TKR without HA Treatment	114 Days														
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HA Course ≥5	1312 Days														
Reference	- Altman R, Lim S, Steen RG, Dasa V. Hyaluronic acid injections are associated with delay of total knee replacement surgery in patients with knee osteoarthritis: evidence from a large U.S. health claims database. <i>PLoS One</i>. 2015;10(12):e0145776. doi:10.1371/journal.pone.0145776 - Jurado RM, Fidalgo AE, Villar VR, Medina JM, López BS. Factors related with the time to surgery in waiting-list patients for knee prostheses. <i>Reumatol Clin</i>. 2013;9(3):148-155. doi: 10.1016/j.reuma.2012.09.003.														

Claim	- For the treatment of OA knee pain: - HA is approved for treating knee OA pain in the United States.¹ - HA, a safe and minimally invasive treatment, is a substance naturally found in the synovial fluid (joint fluid) that lubricates and cushions the joint.¹⁻⁴
Reference	- Bhadra AK, Altman R, Dasa V, et al. Appropriate use criteria for hyaluronic acid in the treatment of knee osteoarthritis in the United States. <i>Cartilage</i>. 2017;8(3):234-54. doi:10.1177/1947603516662503 - Li H, Guo H, Lei C, et al. Nanotherapy in joints: increasing endogenous hyaluronan production by delivering Hyaluronan Synthase 2. <i>Adv Mater</i>. 2019;31(46):e1904535. doi:10.1002/adma.201904535 - Mora JC, Przkora R, Cruz-Almeida Y. Knee osteoarthritis: pathophysiology and current treatment modalities. <i>J Pain Res</i>. 2018;11:2189-96. doi:10.2147/JPR.S154002. - Altman RD, Manjoo A, Fierlinger A, Niazi F, Nicholls M. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. <i>BMC Musculoskelet Disord</i>. 2015;16:321. doi:10.1186/s12891-015-0775-z

Claim	• HMW HA* > 3000 kDa were reported to improve clinical outcomes.¹ [Altman 2019]
Reference	1. Altman R, Bedi A, Manjoo A, Niazi F, Shaw P, Mease P. Anti-inflammatory effects of intra-articular hyaluronic acid: a systematic review. <i>Cartilage</i>. 2019;10(1):43-52. doi:10.1177/1947603517749919 *The study by Altman et al, 2019 does not contain data specific to DUROLANE.

Claim (Patient)	• Did you know HA injections: - o Can relieve OA knee pain for 6 months¹ - o May delay the need for knee replacement surgery^{2,3*} - o Are a natural, non-opioid therapy?⁴ *The study by Altman et al. 2015 does not contain data specific to DUROLANE.
Reference	1. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther</i>. 2015;17(1):51. doi:10.1186/s13075-015-0557-x 2. Altman R, Lim S, Steen RG, Dasa V. Hyaluronic acid injections are associated with delay of total knee replacement surgery in patients with knee osteoarthritis: evidence from a large U.S. health claims database. <i>PLoS One</i>. 2015;10(12):e0145776. doi:10.1371/journal.pone.0145776 3. Jurado RM, Fidalgo AE, Villar VR, Medina JM, López BS. Factors related with the time to surgery in waiting-list patients for knee prostheses. <i>Reumatol Clin</i>. 2013;9(3):148-155. doi:10.1016/j.reuma.2012.09.003 4. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019.

Claim (Patient)	• HA treatments can provide 6 months of OA pain relief with minimal risk of complications.¹⁻⁷ • HA can provide 6 months of OA knee pain relief.¹⁻⁷
Reference	1. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019. 2. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther</i>. 2015;17(1):51. doi:10.1186/s13075-015-0557-x 3. Leighton R, Åkermar C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009 4. Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis.

	<i>Arthritis Rheum.</i> 2009;61(12):1704-11. doi:10.1002/art.24925 5. McGrath AF, McGrath AM, Jessop ZM, et al. A comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. <i>J Arthritis.</i> 2013;2(1):1000108. doi:10.4172/2167-7921.1000108 6. Krocke D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. <i>Z Rheumatol.</i> 2006;65(4):327-31. doi: 10.1007/s00393-006-0063-2 7. Balazs EA, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. <i>J Rheumatol Suppl.</i> 1993;39:3-9.
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8.1. Military Related Claims

These claims address OA in the military.

Claim (Patient)	- Approximately 11,000 new cases of osteoarthritis (OA) are diagnosed each year among 1.3 million active-duty service members.¹ - Service members aged 40 years and older are twice as likely to develop OA than their counterparts in the general population.¹
Reference	1. Cameron KL, Hsiao MS, Owens BD, Burks R, Svoboda SJ. Incidence of physician-diagnosed osteoarthritis among active duty United States military service members. <i>Arthritis Rheum.</i> 2011;63(10):2974-82. doi:10.1002/art.30498

8.2. Alternative Treatment Options for OA

These claims address alternate treatment options for OA, including opioids, intra-articular corticosteroids, and platelet-rich plasma.

8.2.1. Opioids

Claim (Patient)	- Injected opioids are associated with faster progression of degenerative changes in knee osteoarthritis.¹ - Prescription rates for opioids to treat knee OA pain remain significant, at nearly 16% in the United States.²
Reference	1. Bodden J, Joseph GB, Schirò S, et al. Opioid users show worse baseline knee osteoarthritis and faster progression of degenerative changes: a retrospective case-control study based on data from the Osteoarthritis Initiative (OAI). <i>Arthritis Res Ther.</i> 2021;23(1):146. doi:10.1186/s13075-021-02524-9 2. DeMik DE, Bedard NA, Dowdle SB, Burnett RA, McHugh MA, Callaghan JJ. Are we still prescribing opioids for osteoarthritis? <i>J Arthroplasty.</i> 2017;32(12):3578-82.e1. doi:10.1016/j.arth.2017.07.030

8.2.2. Intra-articular Corticosteroids

Claim (Patient)	- Studies have shown that repeated steroid injections can lead to cartilage damage over time.¹ - In patients with mild to moderate knee osteoarthritis, intra-articular corticosteroids (IACs) may be associated with an increased risk of disease progression.² - At 1 year, patients who were treated with IACs showed disease worsening, compared to those who didn't receive the treatment.² - A total of 32% of IAC-treated knees experienced Kellgren-Lawrence grade (KL) worsening after 1 year versus 15% of a comparison cohort without IAC treatment.² - Over the course of the study, 44% of IAC-treated knees experienced Kellgren-Lawrence grade (KL) worsening versus 17% in the comparison cohort without IAC treatment.² - HA has been proven to provide 6 months of pain relief—much longer than steroids.^{3,4}
Reference	- McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. <i>JAMA</i>. 2017;317(19):1967-75. doi:10.1001/jama.2017.5283 - Zeng C, Lane NE, Hunter DJ, et al. Intra-articular corticosteroids and the risk of knee osteoarthritis progression: results from the Osteoarthritis Initiative. <i>Osteoarthritis Cartilage</i>. 2019;27(6):855-62. doi:10.1016/j.joca.2019.01.007 - DUROLANE (package insert). Durham, NC: Bioventus LLC; 2019. - Leighton R, Åkermarck C, Therrien R, et al. NASHA hyaluronic acid vs methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009.

8.2.3. Platelet-Rich Plasma

Claim (Patient)	- Studies have shown mixed results with respect to the effectiveness of platelet-rich plasma (PRP) in treating OA.¹ - There is no established standard for preparation methods, dosages, and frequency of treatment for PRP.¹ - Because of the lack of high-quality evidence and standardization in available preparations, some clinical guidelines recommend against the use of PRP to treat OA.^{1,2}
Reference	- Ding JB, Hu K. Injectable therapies for knee osteoarthritis. <i>Reumatologia</i>. 2021;59(5):330-9. doi:10.5114/reum.2021.110612 - Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. <i>Arthritis Care Res (Hoboken)</i>. 2020;72(2):149-62. doi:10.1002/acr.24131

9. DUROLANE Product Claims

These claims describe DUROLANE and the role of DUROLANE in the treatment of OA.

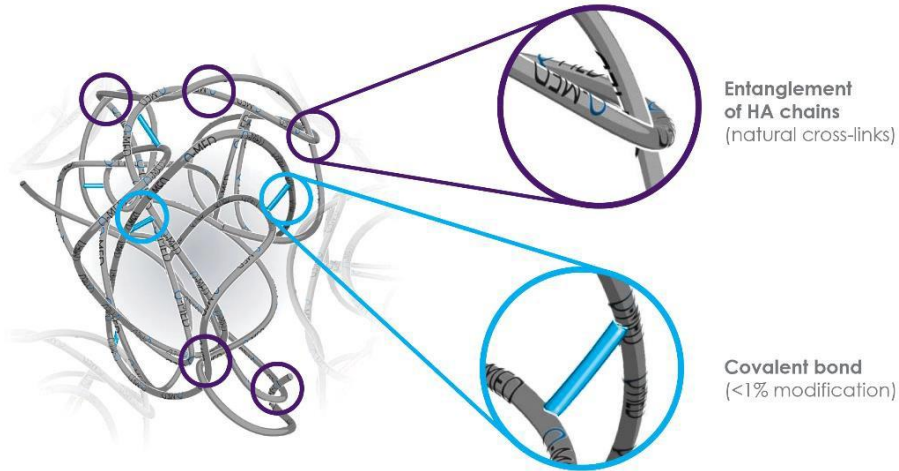
9.1. Product Description/Manufacturing Process

These claims describe DUROLANE and its unique manufacturing process.

Claim[†] <i>Claims followed by † require indication/reference adjustment based on region.</i>	• DUROLANE is supplied as a 3-mL syringe.¹ • DUROLANE is a single-injection course of therapy.¹
Reference	1. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019.

Claim[†] <i>Claims followed by † require indication/reference adjustment based on region.</i>	• DUROLANE contains 20 mg/mL of sodium hyaluronate, dissolved in phosphate buffered saline. The sodium hyaluronate is derived from bacterial fermentation (<i>Streptococcus equi</i>).¹
Reference	1. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019.

Claim	• DUROLANE was designed as a single-injection therapy with unique stabilizing technology.¹ • DUROLANE is a high-molecular-weight, non-avian HA that is stabilized using a carefully controlled cross-linking process to increase residence time in the knee joint.¹⁻³ • DUROLANE uses advanced and unique technology to increase residence time in the joint.¹⁻³ • DUROLANE is designed to resist degradation and prolong knee joint residence time.^{3,4} • DUROLANE is a non-animal, stabilized HA that is cross-linked and entangled to create an HA with a long residence time.¹⁻³ • DUROLANE is stabilized using a carefully controlled cross-linking process, which increases the intra-articular residence time.¹⁻³
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Graphic	 Entanglement of HA chains (natural cross-links) Covalent bond (<1% modification) Entanglement of HA chains (natural cross-links) Covalent bond (<1% modification)
Reference	1. Ågerup B, Berg P, Åkermark C. Non-animal stabilized hyaluronic acid: anew formulation for the treatment of osteoarthritis. <i>BioDrugs</i>. 2005;19(1):23-30. doi:10.2165/00063030-200519010-00003 2. Edsman K, Hjelm R, Lärkner H, et al. Intra-articular duration of Durolane™ after single injection into the rabbit knee. <i>Cartilage</i>. 2011;2(4):384-8. doi:10.1177/1947603511400184 3. Lindqvist U, Tolmachev V, Kairemo K, Åström G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. <i>Clin Pharmacokinet</i>. 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004 4. Edsman K, Melin H, Näsström J. A study of the ability of Durolane™ to withstand degradation by free radicals while maintaining its viscoelastic properties. Poster presented at: 55th Annual Meeting of the Orthopaedic Research Society; February 22-25, 2009; Las Vegas, NV. Poster 1149.

Claim	• DUROLANE has the highest reported molecular weight of any hyaluronic acid indicated for the treatment of knee OA.^{1,2} • The highest reported molecular weight HA product indicated for the treatment of knee OA.¹ • DUROLANE has a molecular weight of 10¹⁵ kDa.¹ • 10¹⁵ kDa molecular weight¹
Reference	1. Bioventus LLC. Q-Med Molecular Weight of DUROLANE. Data on file, RPT-001314. June 2021. 2. Nicholls M, Manjoo A, Shaw P, Niazi F, Rosen J. Rheological properties of commercially available hyaluronic acid products in the United States for the treatment of osteoarthritis knee pain. <i>Clin Med Insights Arthritis Musculoskelet Disord</i>. 2018;11:1179544117751622. doi:10.1177/1179544117751622

Claim	- The molecular weight of DUROLANE can be expressed in the following ways:¹ 1 000 000 000 000 000 000 Da 10¹⁸ Da 10¹⁵ kDa 10¹² MDa
Reference	1. Bioventus LLC. Q-Med Molecular Weight of DUROLANE. Data on file, RPT-001314. June 2021.

Claim	- DUROLANE's technology is unique.¹ - DUROLANE was designed as a single-injection therapy.¹ - Produced through bacterial fermentation.¹ - Biocompatibility maintained through minimal cross-linking.¹
Reference	1. Ågerup B, Berg P, Åkermærk C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. <i>BioDrugs</i> . 2005;19(1):23-30. doi:10.2165/00063030-200519010-00003

Claim	- DUROLANE does not trigger the production of significant levels of antibodies.¹ - DUROLANE does not generate significant levels of antibodies.¹
Reference	1. Wooley PH, Song Z, Harrison A. Hyaluronic acid viscosupplements from avian and non-mammalian sources exhibit biocompatibility profiles with unique, source-specific, antigenic profiles. <i>J Biomed Mater Res B Appl Biomater</i> . 2012;100(3):808-16. doi:10.1002/jbm.b.32514

9.2. Comparative Product Descriptions

These claims compare DUROLANE with other available HA preparations.

Claim	- Unlike Synvisc-One®, DUROLANE does not include HA derived from an avian source.^{1,2} - Unlike Synvisc-One®, DUROLANE is not produced using HA derived from an avian source.^{1,2}
Reference	- DUROLANE [package insert]. Durham, NC. Bioventus LLC; 2019. - Synvisc-One [package insert]. Ridgeway, NJ: Genzyme Biosurgery; 2014.

Claim	Comparison chart^{1,2}															
Graphic	Comparison chart¹⁻² <table><tr><th></th><th>DUROLANE®</th><th>Synvisc-One®</th></tr><tr><td>Injection Volume</td><td>3.0 mL</td><td>6.0 mL</td></tr><tr><td>Concentration</td><td>2.0% HA</td><td>0.8% HA</td></tr><tr><td>HA per Dose</td><td>60 mg</td><td>48 mg</td></tr><tr><td>HA Source</td><td>Biofermentation-derived</td><td>Avian-based</td></tr></table>		DUROLANE®	Synvisc-One®	Injection Volume	3.0 mL	6.0 mL	Concentration	2.0% HA	0.8% HA	HA per Dose	60 mg	48 mg	HA Source	Biofermentation-derived	Avian-based
	DUROLANE®	Synvisc-One®														
Injection Volume	3.0 mL	6.0 mL														
Concentration	2.0% HA	0.8% HA														
HA per Dose	60 mg	48 mg														
HA Source	Biofermentation-derived	Avian-based														
Reference	- Synvisc-One [package insert]. Ridgeway, NJ: Genzyme Biosurgery; 2014. - DUROLANE [package insert]. Durham, NC. Bioventus LLC; 2019.															

Claim	Comparison chart¹⁻¹¹																																								
Graphic	<table><thead><tr><th></th><th>DUROLANE^{®1-5}</th><th>SYNVISC-ONE^{®6-8}</th><th>GEL-ONE^{®9,10}</th><th>MONOVISC^{®11}</th></tr></thead><tbody><tr><td>HA Source</td><td>Bacterial (cross-linked)</td><td>Avian (cross-linked)</td><td>Avian (cross-linked)</td><td>Bacterial (cross-linked)</td></tr><tr><td>Half-life</td><td>Up to 4 weeks or 32 days in the knee^{4,6}</td><td>1.5-8.8 days</td><td>Unknown</td><td>Unknown</td></tr><tr><td>Molecular Weight (daltons)</td><td>10¹²M (>1 billion)*</td><td>6 M</td><td>Unknown</td><td>1.0-2.9 M</td></tr><tr><td>Total Volume (per syringe)</td><td>3.0 mL</td><td>6.0 mL</td><td>3.0 mL</td><td>4.0 mL</td></tr><tr><td>HA Concentration</td><td>2.0% HA</td><td>0.8% HA</td><td>1% HA</td><td>2.2% HA</td></tr><tr><td>Active Ingredient (per treatment)</td><td>60 mg</td><td>48 mg</td><td>30 mg</td><td>88 mg</td></tr><tr><td>Repeat Injection</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr></tbody></table>		DUROLANE ^{®1-5}	SYNVISC-ONE ^{®6-8}	GEL-ONE ^{®9,10}	MONOVISC ^{®11}	HA Source	Bacterial (cross-linked)	Avian (cross-linked)	Avian (cross-linked)	Bacterial (cross-linked)	Half-life	Up to 4 weeks or 32 days in the knee ^{4,6}	1.5-8.8 days	Unknown	Unknown	Molecular Weight (daltons)	10 ¹² M (>1 billion)*	6 M	Unknown	1.0-2.9 M	Total Volume (per syringe)	3.0 mL	6.0 mL	3.0 mL	4.0 mL	HA Concentration	2.0% HA	0.8% HA	1% HA	2.2% HA	Active Ingredient (per treatment)	60 mg	48 mg	30 mg	88 mg	Repeat Injection	Yes	Yes	Yes	Yes
	DUROLANE ^{®1-5}	SYNVISC-ONE ^{®6-8}	GEL-ONE ^{®9,10}	MONOVISC ^{®11}																																					
HA Source	Bacterial (cross-linked)	Avian (cross-linked)	Avian (cross-linked)	Bacterial (cross-linked)																																					
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	<i>Biomater.</i> 2012;100(3):808-16. doi:10.1002/jbm.b.32514. 6. Synvisc-One [package insert]. Ridgeway, NJ: Genzyme Biosurgery; 2014. 7. Chevalier X, Jerosch J, Goupille P, et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. <i>Ann Rheum Dis.</i> 2010;69(1):113-119. doi:10.1136/ard.2008.094623 8. Larsen NE, Dursema HD, Pollak CT, Skrabut EM. Clearance kinetics of a hylan-based viscosupplement after intra-articular and intravenous administration in animal models. <i>J Biomed Mater Res B Appl Biomater.</i> 2012;100(2):457-62. doi:10.1002/jbm.b.31971 9. Gel-One [package insert]. Warsaw, IN: Zimmer; 2011. 10. Strand V, Lim S, Takamura J. Evidence for safety of retreatment with a single intra-articular injection of Gel-200 for treatment of osteoarthritis of the knee from the double-blind pivotal and open-label retreatment clinical trials. <i>BMC Musculoskelet Disord.</i> 2016;17:240. doi:10.1186/s12891-016-1101-0. 11. Monovisc [package insert]. Bedford, MA: Anika Therapeutics, Inc.; 2013.
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Claim	• DUROLANE has a longer half-life than cross-linked Synvisc® (hylan G-F 20).¹⁻³
Reference	1. Edsman K, Hjelm R, Lärkner H, et al. Intra-articular duration of Durolane™ after single injection into the rabbit knee. <i>Cartilage.</i> 2011;2(4):384-8. doi:10.1177/1947603511400184 2. Larsen NE, Dursema HD, Pollak CT, Skrabut EM. Clearance kinetics of a hylan- based viscosupplement after intra-articular and intravenous administration in animal models. <i>J Biomed Mater Res B Appl Biomater.</i> 2012;100(2):457-66. doi:10.1002/jbm.b.31971 3. Lindqvist U, Tolmachev V, Kairemo K, Åstrom G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. <i>Clin Pharmacokinet.</i> 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004

9.3. Half-Life/Residence Time

These claims describe the pharmacokinetic profile of DUROLANE.

Claim	• DUROLANE is stabilized using a carefully controlled cross-linking process with greater resistance to degradation, which increases the intra-articular residence time compared to other HA preparations.^{1-3*} • DUROLANE has the longest reported total joint residence time compared to other leading HA preparations.^{1-3*} • DUROLANE uses advanced and unique NASHA technology to increase residence time in the joint.^{1-3*} *Add Note: <i>Preclinical residence time has not been correlated with the duration of clinical effect.</i>
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Reference	1. Agerup B, Berg P, Åkermark C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. <i>BioDrugs</i>. 2005;19(1):23-30. doi:10.2165/00063030-200519010-00003 2. Edsman K, Hjelm R, Lärkner H, et al. Intra-articular duration of Durolane™ after single injection into the rabbit knee. <i>Cartilage</i>. 2011;2(4)384-8. doi:10.1177/1947603511400184 3. Lindqvist U, Tolmachev V, Kairemo K, Åström G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. <i>Clin Pharmacokinet</i>. 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004
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Claim	• DUROLANE has a half-life of 32 days in the animal joint following a single injection.^{1*} *Add Note: <i>Preclinical residence time has not been correlated with the duration of clinical effect.</i>
Reference	1. Edsman K, Hjelm R, Lärkner H, et al. Intra-articular duration of Durolane™ after single injection into the rabbit knee. <i>Cartilage</i>. 2011;2(4)384-8. doi:10.1177/1947603511400184

Claim	• DUROLANE has a half-life of approximately 4 weeks or 30 days in the knee joint in a single-injection regimen.¹ • DUROLANE has a half-life of approximately 4 weeks in a human joint in a single-injection treatment regimen.¹
Reference	1. Lindqvist U, Tolmachev V, Kairemo K, Åström G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. <i>Clin Pharmacokinet</i>. 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004

Claim	• DUROLANE has a longer half-life than unstabilized HA.^{1-2*} *Add Note: <i>Preclinical residence time has not been correlated with the duration of clinical effect.</i>
Reference	1. Brown TJ, Laurent UB, Fraser JR. Turnover of hyaluronan in synovial joints: elimination of labelled hyaluronan from the knee joint of the rabbit. <i>Exp Physiol</i>. 1991;76(1):125-34. doi:10.1113/expphysiol.1991.sp003474 2. Edsman K, Hjelm R, Lärkner H, et al. Intra-articular duration of Durolane™ after single injection into the rabbit knee. <i>Cartilage</i>. 2011;2(4)384-8. doi:10.1177/1947603511400184

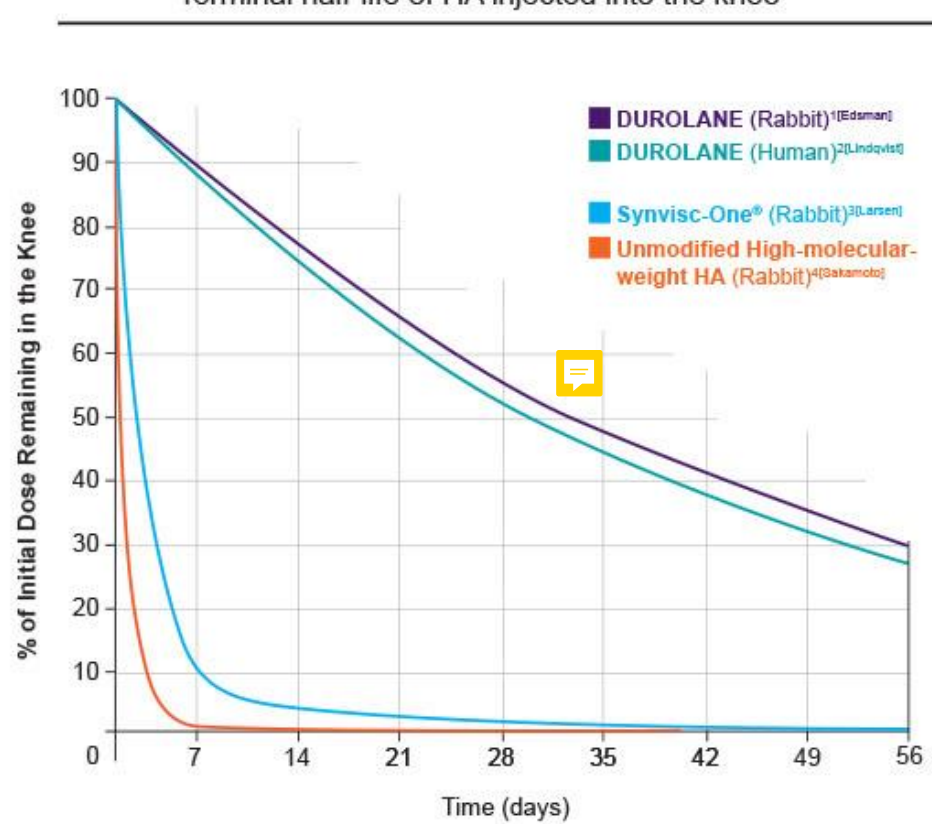
Claim	DUROLANE has a longer half-life than cross-linked Synvisc® (hylan G-F 20).^{1-3*} *Add Note: <i>Preclinical residence time has not been correlated with the duration of clinical effect.</i>
Reference	- Edsman K, Hjelm R, Lärkner H, et al. Intra-articular duration of Durolane™ after single injection into the rabbit knee. <i>Cartilage</i>. 2011;2(4)384-8. doi:10.1177/1947603511400184 - Larsen NE, Dursema HD, Pollak CT, Skrabut EM. Clearance kinetics of a hylan- based viscosupplement after intra-articular and intravenous administration in animal models. <i>J Biomed Mater Res B Appl Biomater</i>. 2012;100(2):457-66. doi:10.1002/jbm.b.31971 - Lindqvist U, Tolmachev V, Kairemo K, Åstrom G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. <i>Clin Pharmacokinet</i>. 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004

Claim	DUROLANE has a longer half-life than unstabilized hyaluronic acid (HA) and cross-linked Synvisc-One® (hylan G-F 20).^{1-4*} *Add Note: <i>Preclinical residence time has not been correlated with the duration of clinical effect.</i> NOTE: Each of the two comparisons need to always be associated with their respective references.
Reference	- Brown TJ, Laurent UB, Fraser JR. Turnover of hyaluronan in synovial joints: elimination of labelled hyaluronan from the knee joint of the rabbit. <i>Exp Physiol</i>. 1991;76(1):125-34. doi:10.1113/expphysiol.1991.sp003474 - Edsman K, Hjelm R, Lärkner H, et al. Intra-articular duration of Durolane™ after single injection into the rabbit knee. <i>Cartilage</i>. 2011;2(4)384-8. doi:10.1177/1947603511400184 - Lindqvist U, Tolmachev V, Kairemo K, Åstrom G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. <i>Clin Pharmacokinet</i>. 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004 - Larsen NE, Dursema HD, Pollak CT, Skrabut EM. Clearance kinetics of a hylan- based viscosupplement after intra-articular and intravenous administration in animal models. <i>J Biomed Mater Res B Appl Biomater</i>. 2012;100(2):457-66. doi:10.1002/jbm.b.31971

Claim	- DUROLANE is manufactured with NASHA technology to resist degradation and prolong joint residence time.^{1,2*} - DUROLANE has a total joint residence time of approximately 150 days^{1,2*} based on a half-life of 30 days.^{1,2*}
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	*Add Note: <i>Preclinical residence time has not been correlated with the duration of clinical effect.</i>
Reference	- Edsman K, Melin H, Nasstrom J. A study of the ability of Durolane™ to withstand degradation by free radicals while maintaining its viscoelastic properties. Poster presented at: 55th Annual Meeting of the Orthopaedic Research Society; February 22-25, 2009; Las Vegas, NV. Poster 1149. - Lindqvist U, Tolmachev V, Kairemo K, Åström G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. <i>Clin Pharmacokinet.</i> 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004

Claim	- DUROLANE has a half-life of approximately 4 weeks in a human joint with a single-injection treatment regimen.¹ - DUROLANE has a half-life of 30 days in the human joint with a single-injection treatment regimen.¹ - DUROLANE has a longer half-life than unstabilized HA or cross-linked Synvisc-One® (hylan G-F 20).^{1-4*} - DUROLANE has the longest reported half-life of any leading HA.^{1-4*} *Add Note: <i>Preclinical residence time has not been correlated with the duration of clinical effect.</i>
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Graph [Edsman 2011: 4a; Lindqvist 2002: 1a- b; Larsen 2012: 1a; Sakamoto 1984: 1a,5a]	Terminal half-life of HA injected into the knee*  The graph illustrates the percentage of initial dose remaining in the knee over time for four different hyaluronic acid (HA) products. DUROLANE (Rabbit) and DUROLANE (Human) maintain a higher percentage of the initial dose over time compared to Synvisc-One® (Rabbit) and Unmodified High-molecular-weight HA (Rabbit). A yellow comment icon is present near the DUROLANE (Human) curve at day 35. <table><caption>Estimated data points from the graph</caption><tr><th>Time (days)</th><th>DUROLANE (Rabbit)¹[Edsman]</th><th>DUROLANE (Human)²[Lindqvist]</th><th>Synvisc-One® (Rabbit)³[Larsen]</th><th>Unmodified High-molecular-weight HA (Rabbit)⁴[Sakamoto]</th></tr><tr><td>0</td><td>100</td><td>100</td><td>100</td><td>100</td></tr><tr><td>7</td><td>~90</td><td>~85</td><td>~15</td><td>~5</td></tr><tr><td>14</td><td>~80</td><td>~75</td><td>~5</td><td>~2</td></tr><tr><td>21</td><td>~70</td><td>~65</td><td>~2</td><td>~1</td></tr><tr><td>28</td><td>~60</td><td>~55</td><td>~1</td><td>~0.5</td></tr><tr><td>35</td><td>~50</td><td>~45</td><td>~0.5</td><td>~0.2</td></tr><tr><td>42</td><td>~40</td><td>~35</td><td>~0.2</td><td>~0.1</td></tr><tr><td>49</td><td>~30</td><td>~25</td><td>~0.1</td><td>~0.05</td></tr><tr><td>56</td><td>~20</td><td>~15</td><td>~0.05</td><td>~0.02</td></tr></table>	Time (days)	DUROLANE (Rabbit) ¹ [Edsman]	DUROLANE (Human) ² [Lindqvist]	Synvisc-One® (Rabbit) ³ [Larsen]	Unmodified High-molecular-weight HA (Rabbit) ⁴ [Sakamoto]	0	100	100	100	100	7	~90	~85	~15	~5	14	~80	~75	~5	~2	21	~70	~65	~2	~1	28	~60	~55	~1	~0.5	35	~50	~45	~0.5	~0.2	42	~40	~35	~0.2	~0.1	49	~30	~25	~0.1	~0.05	56	~20	~15	~0.05	~0.02
Time (days)	DUROLANE (Rabbit) ¹ [Edsman]	DUROLANE (Human) ² [Lindqvist]	Synvisc-One® (Rabbit) ³ [Larsen]	Unmodified High-molecular-weight HA (Rabbit) ⁴ [Sakamoto]																																															
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42	~40	~35	~0.2	~0.1																																															
49	~30	~25	~0.1	~0.05																																															
56	~20	~15	~0.05	~0.02																																															

Reference	1. Edsman K, Hjelm R, Lärkner H, et al. Intra-articular duration of Durolane™ after single injection into the rabbit knee. <i>Cartilage</i>. 2011;2(4):384-8. doi:10.1177/1947603511400184 2. Lindqvist U, Tolmachev V, Kairemo K, Åström G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. <i>Clin Pharmacokinet</i>. 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004 3. Larsen NE, Dursema HD, Pollak CT, Skrabut EM. Clearance kinetics of a hylan-based viscosupplement after intra-articular and intravenous administration in animal models. <i>J Biomed Mater Res B Appl Biomater</i>. 2012;100(2):457-62. doi:10.1002/jbm.b.31971 4. Sakamoto T. Biological fate of sodium hyaluronate (SPH) (1) Studies on distribution, metabolism and excretion of 14C-SPH in rabbits after intra-articular administration. <i>Pharmacometrics</i>. 1984;28(2):375-87.
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9.4. Ease of Administration

These claims address the administration of DUROLANE.

Claim	• DUROLANE is a transparent, viscoelastic gel.¹ • Transparent viscoelastic gel supplied in a 3-mL glass syringe¹ • DUROLANE is available in a 3-mL size.¹ • DUROLANE is a single-injection therapy.¹
Reference	1. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019.

Claim	• DUROLANE was designed as a single-injection course of therapy.¹ • DUROLANE was designed as a single-injection therapy.¹
Reference	1. Ågerup B, Berg P, Åkermark C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. <i>BioDrugs</i> . 2005;19(1):23-30. doi:10.2165/00063030-200519010-00003

9.5. DUROLANE Product and Clinical Benefit Claims (Combined)

These claims address the DUROLANE product and its clinical benefits.

Claim	• 20+ clinical studies investigate the use of DUROLANE in the knee.¹
Reference	1. Bioventus. Data on File. RPT-001367. Accessed 06/2022.

Claim	• DUROLANE is a single-injection HA designed to deliver powerful, long-lasting osteoarthritis (OA) knee pain relief.¹⁻⁶ • DUROLANE is a one-injection HA treatment designed to deliver powerful, long-lasting knee OA pain relief.¹⁻⁶ • DUROLANE was designed as a single-injection treatment for convenient, long-lasting treatment.¹⁻⁶ • Helps relieve painful knee osteoarthritis (OA) with a single-injection treatment.¹⁻⁶ • DUROLANE is a single-injection treatment designed to provide long-lasting relief of OA knee pain.¹⁻⁶ NOTE: Between Leighton, McGrath, and Zhang references - One or all references can be used to support the specific claims; do not need all three references every time.
Reference	1. McGrath AF, McGrath AM, Jessop ZM, et al. A comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. <i>J Arthritis</i>. 2013;2(1):1000108. doi:10.4172/2167-7921.1000108 2. Leighton R, Åkermarck C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009 3. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther</i>. 2015;17:51. doi:10.1186/s13075-015-0557-x 4. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019. 5. Ågerup B, Berg P, Åkermarck C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. <i>BioDrugs</i>. 2005;19(1):23-30. doi:10.2165/00063030-200519010-00003 6. Krocke D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. <i>Z Rheumatol</i>. 2006;65(4):327-31. doi:10.1007/s00393-006-0063-2

Claim (Patient)	• What is DUROLANE? - o DUROLANE is a single-injection HA treatment designed to provide powerful and lasting pain relief when you are suffering from knee pain due to OA.¹⁻⁴ • What are the benefits of DUROLANE? - o DUROLANE reduces knee joint pain for up to 6 months, and improves physical activity and quality of life of knee OA patients in as early as 2 weeks, for up to 24 weeks.¹⁻⁴ • Is DUROLANE right for me? - o If you are an OA patient who is not getting enough knee pain relief from oral medications, physical therapy or steroids, DUROLANE might be
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	right for you.⁵ Speak with your doctor about HA treatment with DUROLANE. - Is there any reason why I couldn't have a DUROLANE injection? - You should not use DUROLANE if you have infections or skin disease at the injection site. DUROLANE has not been tested in pregnant or lactating women, or children.⁵ - Full indication and contraindication information can be found in prescribing information, at www.durolane.com or by contacting Bioventus Customer Service at 1-800-836-4080.⁵
Reference	- Leighton R, Åkermarck C, Therrien R, et al. NASHA hyaluronic acid vs methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009 - Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. <i>Arthritis Rheum</i>. 2009;61(12):1704-11. doi:10.1002/art.24925 - McGrath AF, McGrath AM, Jessop ZM, et al. A comparison of intra- articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. <i>J Arthritis</i>. 2013;2(1):1000108. doi:10.4172/2167-7921.1000108 - Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. <i>Z Rheumatol</i>. 2006;65(4):327-31. doi:10.1007/s00393-006-0063-2 - DUROLANE [package insert]. Durham, NC: Bioventus LLC, 2019.

9.6. DUROLANE Clinical Effectiveness Claims

These claims address the clinical effectiveness of DUROLANE, including clinical trial design and key results.

9.6.1. Clinical Study Designs

Claim	- A pivotal, non-inferiority trial compared one intra-articular injection of DUROLANE with a five-injection course of therapy with another HA.¹ - The multicenter, randomized double-blind non-inferiority trial involved 349 patients with mild to moderate osteoarthritis of the knee. - The primary efficacy variable was the Likert-type WOMAC pain scale at baseline and at 6, 10, 14, 18, and 26 weeks.¹ - Secondary efficacy variables were change from baseline scores of the WOMAC physical function and knee stiffness subscales, and global self-assessment.¹
Reference	Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther</i>. 2015;17:51. doi:10.1186/s13075-015-0557-x

Claim	• A prospective, randomized, non-inferiority trial compared one intra-articular injection of DUROLANE with an injection of methylprednisolone acetate (MPA).¹ • The multicenter, randomized double-blind non-inferiority trial involved 442 patients with mild to moderate osteoarthritis of the knee.¹ • The primary efficacy endpoint was the Likert-type WOMAC pain scale responder rate at 12 weeks.¹ • Secondary efficacy variables included change from baseline scores of the WOMAC pain, physical function, and knee stiffness subscales; global self-assessment; OMERACT-OARSI responder rate; and use of rescue medication.¹
Reference	1. Leighton R, Åkermarck C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009

9.6.2. Equivalence / Non-inferiority

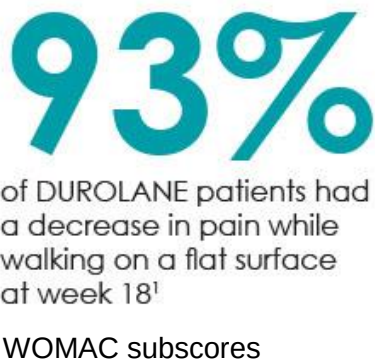
Claim	• DUROLANE is the only single-injection HA proven to be clinically equivalent to a five-injection therapy.^{1,2} • In a Level 1 study, one injection of DUROLANE produced pain reduction at 6 months that was noninferior to the relief achieved with five injections of the comparator HA.¹ ◦ 79% of patients treated with DUROLANE experienced pain control for up to 26 weeks.¹ • In a pivotal non-inferiority study, one injection of DUROLANE produced clinically equivalent pain relief at 6 months to relief achieved with five injections of the comparator HA.^{1,2}
Reference	1. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther</i>. 2015;17:51. doi:10.1186/s13075-015-0557-x 2. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019.

Claim	• In a Level 1 study, one injection of DUROLANE produced pain reduction at 12 weeks that was noninferior to the relief achieved with an injection of MPA.¹ ◦ 45% of patients treated with DUROLANE experienced pain control for 12 weeks.¹ ◦ This effect was sustained 26 weeks after the initial injection.¹ • In a non-inferiority study, one injection of DUROLANE produced clinically equivalent pain relief at 12 weeks to relief achieved with a corticosteroid injection.^{1,2}
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	o The benefit of DUROLANE was maintained at 26 weeks, while the benefit of the corticosteroid injection declined.¹
Reference	1. Leighton R, Åkermarck C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009

9.6.3. Pain Relief

Claim	• DUROLANE delivers powerful, long-lasting pain relief.¹⁻⁵ - o Nearly 8 in 10 patients (79%) experienced improved pain control over baseline for 26 weeks.¹ • 26 weeks of pain relief over baseline.¹⁻³ - o In a pivotal, non-inferiority study, nearly 8 in 10 patients treated with DUROLANE experienced improved pain control for 26 weeks over baseline, assessed with the visual analog scale.¹ • 26 weeks of pain relief over baseline in a pivotal, non-inferiority study¹
Graphic [Zhang 2015: 7a]	 The graphic consists of two main parts. On the left, the text '26 WEEKS OF PAIN RELIEF OVER BASELINE' is displayed in a blue and black sans-serif font. On the right, there is a purple circular badge containing the text '79%' in white. To the right of the badge, a purple arrow points to the right, containing the text 'of patients experienced improved pain control for 26 weeks over baseline' in white.
Reference	1. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther</i>. 2015;17:51. doi:10.1186/s13075-015-0557-x 2. Leighton R, Åkermarck C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009 3. McGrath AF, McGrath AM, Jessop ZM, et al. A comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. <i>J Arthritis</i>. 2013;2(1):1000108. doi:10.4172/2167-7921.1000108 4. Krocke D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. <i>Z Rheumatol</i>. 2006;65(4):327-31. doi:10.1007/s00393-006-0063-2 5. Leighton R, Fitzpatrick J, Smith H, Crandall D, Flannery CR, Conrozier T. Systematic clinical evidence review of NASHA (Durolane hyaluronic acid) for the treatment of knee osteoarthritis. <i>Open Access Rheumatol</i>. 2018;10:43-54. doi:10.2147/OARRR.S162127

Claim	93% of DUROLANE-treated patients had a decrease in pain while walking on a flat surface at week 18.¹
Graphic [Zhang 2015: 7b]	
Reference	Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther.</i> 2015;17:51. doi:10.1186/s13075-015-0557-x

Claim	Approximately 9 in 10 patients treated with DUROLANE felt reduced pain walking on a flat surface at week 26.¹ [Zhang 2015: 7b-c]
Graphic [Zhang 2015: 7b- c]	
Reference	Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther.</i> 2015;17:51. doi:10.1186/s13075-015-0557-x

Claim	One injection of DUROLANE provided up to 6 months of pain relief over baseline, reducing the need for rescue medications.¹
Reference	Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther.</i> 2015;17:51. doi:10.1186/s13075-015-0557-x

9.6.4. Improved Function

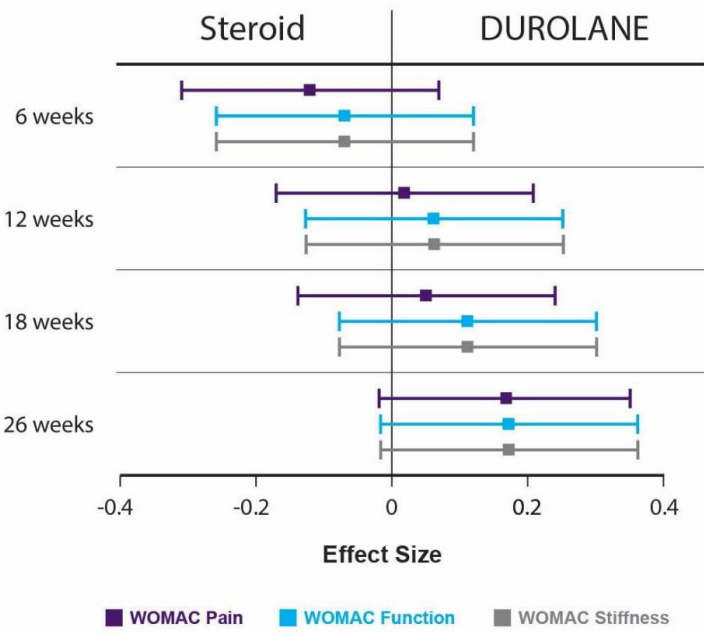
Claim	- Improved knee function: - Physical function improved 59% at 26 weeks among patients in the DUROLANE treatment group ($p < 0.0001$) over baseline.¹ - Patient reported physical function improved by 59% at 26 weeks over baseline.¹
Reference	Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther.</i> 2015;17:51. doi:10.1186/s13075-015-0557-x

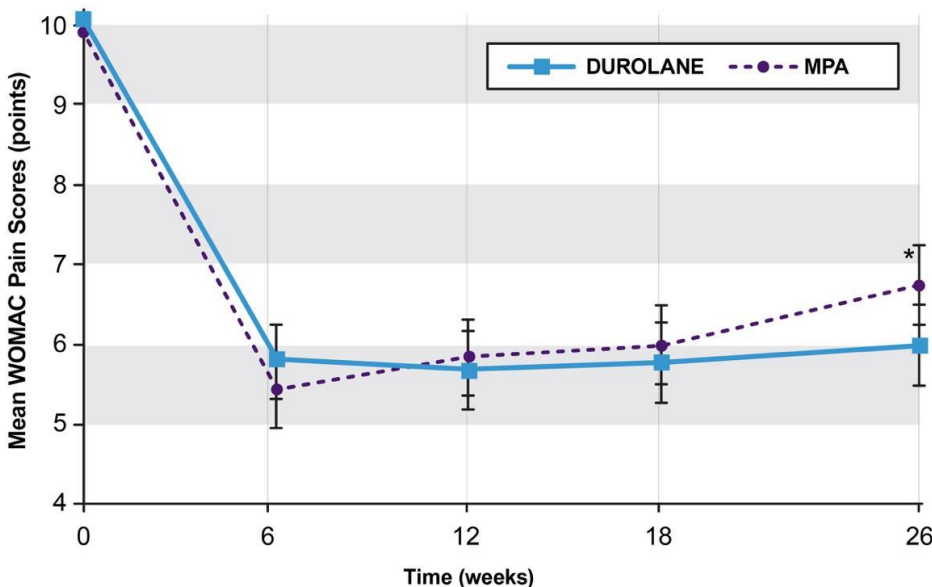
Claim	- Two weeks after a DUROLANE injection, subjective evaluations of knee function that measured activities of daily living and sports/leisure activities improved significantly over baseline ($p < 0.001$ for both).¹ - Significant improvement over baseline was seen in as little as two weeks post-injection in all Knee Injury and Osteoarthritis Outcome Score (KOOS) parameters, including activities of daily living ($p < 0.001$) and sports/leisure activities ($p < 0.001$).¹
Reference	Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. <i>Z Rheumatol.</i> 2006;65(4):327-31. doi:10.1007/s00393-006-0063-2

9.7. Comparative Studies - Efficacy and Safety

These claims address the comparative efficacy and safety of DUROLANE with other standard of care treatments for OA.

Claim	- In a Level 1 study, the effects of DUROLANE were longer lasting than the steroid MPA cohort, demonstrated by the significant difference in OMERACT-OARSI responder rate at 26 weeks ($p = 0.0237$).¹ - Longer-lasting knee pain relief versus MPA^{1*} - Longer-lasting knee pain relief versus steroid^{1*} Add Note: <i>*Based on OMERACT-OARSI responder rate at 26 weeks; Methylprednisolone acetate (MPA)</i>
Reference	Leighton R, Åkermarm C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage.</i> 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009

Claim	- Longer-lasting knee pain relief versus steroid^{1*} - In a Level 1 study: - DUROLANE was proven to be noninferior to steroid at 6 weeks^{†1} - Results favored DUROLANE for WOMAC pain, function, and stiffness scores from 12-26 weeks¹ - Significant reduction in WOMAC pain from baseline at 26 weeks¹ - Significant reduction in WOMAC pain scores from baseline with DUROLANE versus steroid at week 26 ($p=0.034$)¹ Add Note: <i>*Based on OMERACT-OARSI responder rate at 26 weeks; Methylprednisolone acetate (MPA).</i> <i>†The primary outcome was the WOMAC pain responder rate at 12 weeks, defined as at least 40% relative improvement and 5-point absolute improvement from baseline values.¹</i>
Graphic [Leighton 2014: 6a]	 Effect-sizes for WOMAC domains with 95% CIs during the blinded phase of the study.
Reference	Leighton R, Åkermarck C, Therrien R, et al. NASHA hyaluronic acid vs methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009

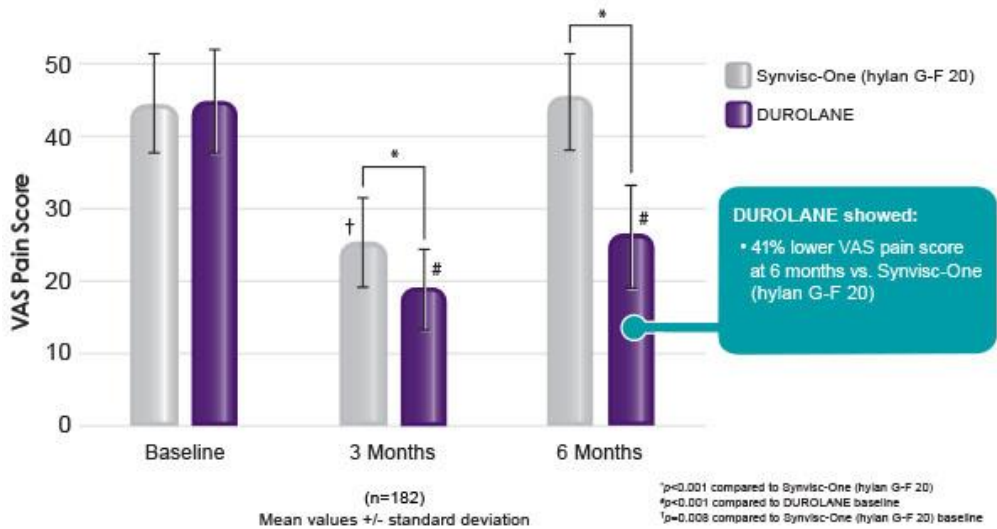
Claim	• More powerful, lasting pain relief versus MPA at 26 weeks in a prospective, randomized study.¹ • DUROLANE is as effective as MPA at 6 weeks for WOMAC pain responder rate.^{†1} • MPA reached maximum effect on mean WOMAC pain scores at 6 weeks.¹ • Results trended in favor of DUROLANE for WOMAC pain, physical function, and stiffness from 12-26 weeks.¹ Add Note: [†]WOMAC pain responder rate was defined as a relative improvement from baseline in WOMAC pain score of at least 40%, and an absolute improvement of at least five points.
Graph [Leighton 2014: 5c,d]	 WOMAC pain scores ($\pm$ 95% CIs) following double-blind treatment with either DUROLANE or MPA. Add Note: *Significant improvement from baseline with DUROLANE vs. MPA at week 26 ($p=0.034$).
Reference	1. Leighton R, Åkermark C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009

Claim	• More powerful pain relief* versus Synvisc-One^{®†} (hylan G-F 20) in a prospective, randomized study.¹ Add Note:
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	<i>*Up to 6 months based on VAS values.</i> <i>†Study references Synvisc & Synvisc-One, 3 injections of Synvisc is equivalent in volume to 1 injection of Synvisc-One.</i>
Reference	1. McGrath AF, McGrath AM, Jessop ZM, et al. A comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. <i>J Arthritis</i>. 2013;2(1):1000108. doi:10.4172/2167-7921.1000108

Claim	- A single-injection hyaluronic acid (HA) treatment that has proven: - Greater reduction in knee pain* versus Synvisc-One^{®†} (hylan G-F 20)¹ - Longer lasting pain relief versus steroid at 26 weeks.² - Clinically equivalent performance to five-injection HA therapy^{3,4} Add Note: <i>*Up to 6 months based on VAS values.</i> <i>†Study references Synvisc & Synvisc-One, 3 injections of Synvisc is equivalent in volume to 1 injection of Synvisc-One.</i>
Reference	1. McGrath AF, McGrath AM, Jessop ZM, et al. A comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. <i>J Arthritis</i>. 2013;2(1):1000108. doi:10.4172/2167-7921.1000108 2. Leighton R, Åkermarck C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009 3. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther</i>. 2015;17:51. doi:10.1186/s13075-015-0557-x 4. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019.

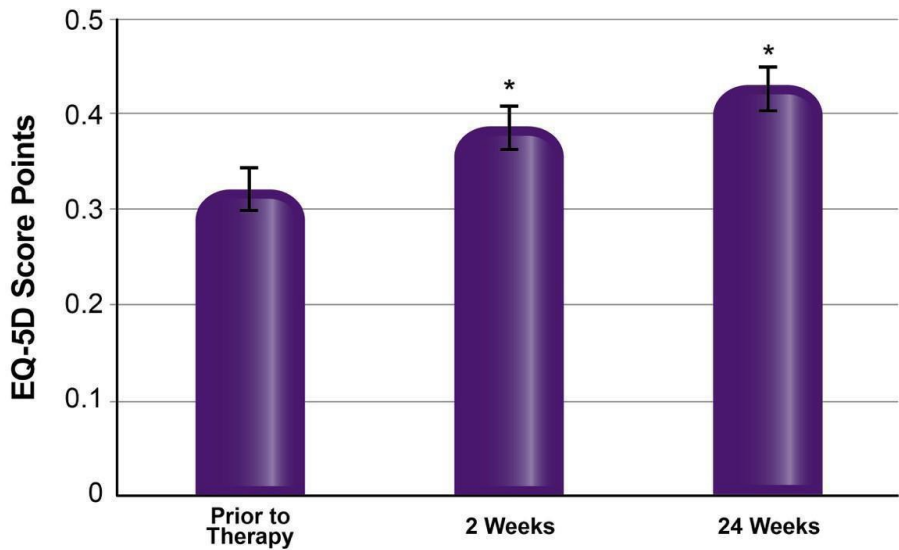
Claim	- DUROLANE offers pain relief* in a prospective, randomized, head-to-head study versus Synvisc-One^{®†1} - More powerful pain relief* versus Synvisc-One^{®†} (hylan G-F 20) in a prospective randomized study.¹ - Greater reduction in knee pain* versus Synvisc-One^{®†} (hylan G-F 20)¹ - In a study with mild to moderate knee OA patients, the reduction in pain at 6 months post-injection was significant with DUROLANE, compared to Synvisc-One^{®†} at 6 months, which did not significantly reduce pain* ($p < 0.001$ and $p = 0.783$, respectively).¹ - Patients treated with DUROLANE reported a 41% reduction in pain at 6
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	months on the visual analog scale ($p < 0.001$).¹ - Reduction in VAS pain score at 3 and 6 months was significantly greater with DUROLANE than with Synvisc-One^{®†} (hylan G-F 20) ($p < 0.001$).¹ - Significant reduction in analgesia use for up to 9 months in patients treated with DUROLANE ($p < 0.001$).¹ - In a prospective randomized study, reduction in visual analog scale (VAS) pain scores at 3 and 6 months was significantly greater with DUROLANE compared to Synvisc-One^{®†} (hylan G-F 20) ($p < 0.001$).¹ - DUROLANE showed: 41% lower VAS pain score at 6 months versus Synvisc-One^{®†} (hylan G-F 20)¹ Add Note: <i>*Up to 6 months based on VAS values.</i> <i>†Study references Synvisc & Synvisc-One, 3 injections of Synvisc is equivalent in volume to 1 injection of Synvisc-One.</i>
Graphic [McGrath 2013: 2i]	 Mean values $\pm$ standard deviation (n=182) Legend: Synvisc-One (hylan G-F 20) (grey), DUROLANE (purple) DUROLANE showed: 41% lower VAS pain score at 6 months vs. Synvisc-One (hylan G-F 20) Significance markers: * $p < 0.001$ compared to Synvisc-One (hylan G-F 20); # $p < 0.001$ compared to DUROLANE baseline; † $p = 0.008$ compared to Synvisc-One (hylan G-F 20) baseline.
Reference	McGrath AF, McGrath AM, Jessop ZM, et al. A comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. <i>J Arthritis</i>. 2013;2(1):1000108. doi:10.4172/2167-7921.1000108

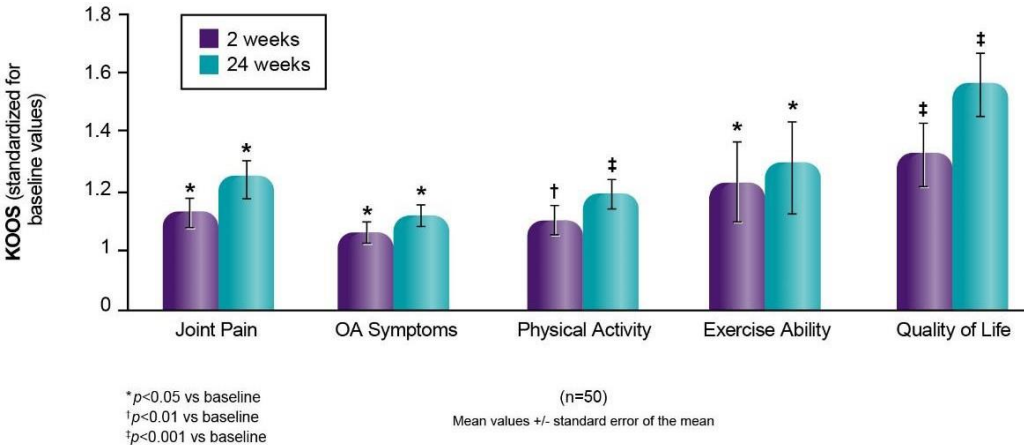
9.8. Quality of Life Benefits

These claims address the quality of life benefits related to DUROLANE in clinical trials.

Claim	- DUROLANE significantly improved quality of life in as early as 2 weeks, up to 24 weeks.¹ - Powerful and lasting improvement in quality of life seen through 24 weeks.¹ - DUROLANE has been proven to significantly improve quality of life in as
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	early as 2 weeks, up to 24 weeks.¹ • DUROLANE has been shown to provide powerful results for improving quality of life through 24 weeks.¹ • DUROLANE significantly improved mean EQ-5D scores over baseline by 21% and 36% at week 2 and 24 respectively, following a single injection ($p<0.001$).¹
Graphic [Krocker 2006: 2e]	 EQ-5D Score Points Prior to Therapy 2 Weeks 24 Weeks <i>Quality of life measured using the EQ-5D questionnaire prior to therapy and at follow-up visits.</i> Mean values $\pm$ SEM $*p<0.001$
Reference	1. Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. <i>Z Rheumatol.</i> 2006;65(4):327-31. doi:10.1007/s00393-006-0063-2

Claim	• A single injection of DUROLANE significantly improved all Knee Injury and Osteoarthritis Outcome Score (KOOS) parameters as early as 2 weeks and continued for up to 24 weeks.¹ • A single injection of DUROLANE significantly reduced knee pain at 24-week follow-up ($p<0.001$).¹ • Two weeks after a DUROLANE injection, subjective evaluations of knee function and quality of life improved significantly.¹ • Significant improvement in all Knee Injury and Osteoarthritis Outcome Score (KOOS) parameters from 2 weeks.¹
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Graphic [Krocker 2006: 2d]	 KOOS, Knee Injury and Osteoarthritis Outcome Score.
Reference	1. Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. <i>Z Rheumatol.</i> 2006;65(4):327-31. doi:10.1007/s00393-006-0063-2

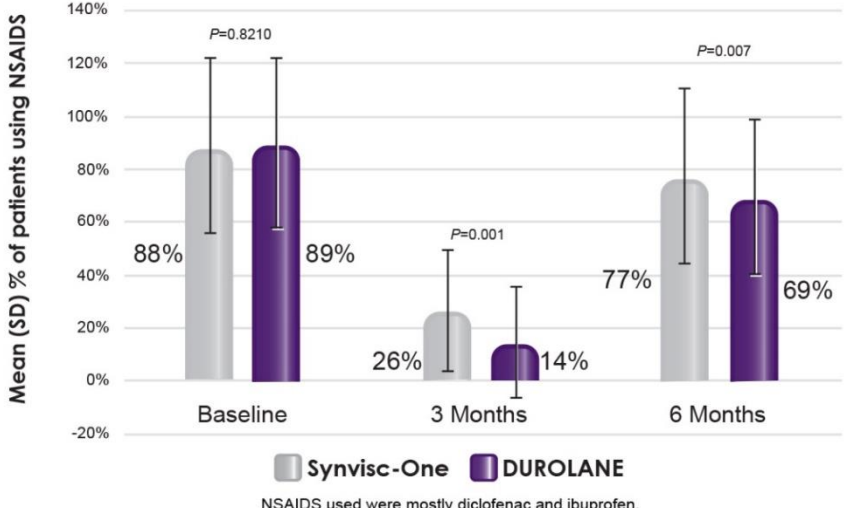
Claim	• Powerful and lasting improvement in quality of life demonstrated as early as 2 weeks and continued for up to 24 weeks.¹
Reference	1. Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated kneepain through a single intra-articular injection of synthetic hyaluronic acid. <i>Z Rheumatol.</i> 2006;65(4):327-31. doi:10.1007/s00393-006-0063-2

9.9. Reduction in Pain Medication

These claims address the effect of DUROLANE on the use of analgesics for OA.

Claim	• DUROLANE has been shown to reduce the use of oral analgesics.^{1,2}
Reference	1. Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. <i>Z Rheumatol.</i> 2006;65(4):327-31. doi:10.1007/s00393-006-0063-2 2. McGrath AF, McGrath AM, Jessop ZM, et al. A Comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. <i>J Arthritis.</i> 2013;2(1):1000108. doi:10.4172/2167-7921.1000108

Claim	DUROLANE provides a significant reduction in analgesia use ($p=0.004$).¹									
Graphic [Krocker 2006: 3f]	Significant Reduction in Analgesic Use¹ <table><tr><th>Mean Values</th><th>Weeks 1 - 2</th><th>Weeks 3 - 24</th></tr><tr><td>Analgesic</td><td>0.77 g/wk</td><td>0.33 g/wk</td></tr><tr><td>p-value</td><td>—</td><td>$p=0.004$</td></tr></table>	Mean Values	Weeks 1 - 2	Weeks 3 - 24	Analgesic	0.77 g/wk	0.33 g/wk	p -value	—	$p=0.004$
Mean Values	Weeks 1 - 2	Weeks 3 - 24								
Analgesic	0.77 g/wk	0.33 g/wk								
p -value	—	$p=0.004$								
Reference	1. Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. <i>Z Rheumatol.</i> 2006;65(4):327-31. doi:10.1007/s00393-006-0063-2									

Claim	Significant reduction of NSAID use with DUROLANE at 3 months and at 6 months compared with Synvisc-One^{®†} (hylan G-F 20).¹ Add Note: [†]Study references Synvisc & Synvisc-One, 3 injections of Synvisc is equivalent in volume to 1 injection of Synvisc-One.																
Graph [McGrath 2013: 3e]	NSAID Use (%)  <table><caption>NSAID Use (%) Data</caption><thead><tr><th>Time Point</th><th>Synvisc-One (%)</th><th>DUROLANE (%)</th><th>P-value</th></tr></thead><tbody><tr><td>Baseline</td><td>88%</td><td>89%</td><td>$P=0.8210$</td></tr><tr><td>3 Months</td><td>26%</td><td>14%</td><td>$P=0.001$</td></tr><tr><td>6 Months</td><td>77%</td><td>69%</td><td>$P=0.007$</td></tr></tbody></table> ■ Synvisc-One ■ DUROLANE NSAIDs used were mostly diclofenac and ibuprofen.	Time Point	Synvisc-One (%)	DUROLANE (%)	P-value	Baseline	88%	89%	$P=0.8210$	3 Months	26%	14%	$P=0.001$	6 Months	77%	69%	$P=0.007$
Time Point	Synvisc-One (%)	DUROLANE (%)	P-value														
Baseline	88%	89%	$P=0.8210$														
3 Months	26%	14%	$P=0.001$														
6 Months	77%	69%	$P=0.007$														

Reference	1. McGrath AF, McGrath AM, Jessop ZM, et al. A Comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. <i>J Arthritis</i> . 2013;2(1):1000108. doi:10.4172/2167-7921.1000108
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Claim	One injection of DUROLANE provided up to 6 months of pain relief, reducing the need for rescue medications.
Reference	1. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther</i> . 2015;17:51. doi:10.1186/s13075-015-0557-x

Claim	- Only 5 of 100 patients used additional pain medication in the 10-to-18-week period following DUROLANE treatment.¹ [Zhang 2015: 7b-c] 95% of patients did not require additional pain medication from 10-18weeks after treatment¹. [Zhang 2015: 7b-c]
Graphic [Zhang 2015: 7b-c]	 95% of patients did not require additional pain medication from 10-18 weeks after treatment
Reference	1. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther</i> . 2015;17:51. doi:10.1186/s13075-015-0557-x.

9.10. Safety and Efficacy

These claims address the safety and efficacy of DUROLANE in clinical trials.

Claim	DUROLANE has proven safety and efficacy in knee osteoarthritis.¹
Reference	1. Leighton R, Fitzpatrick J, Smith H, Crandall D, Flannery CR, Conrozier T. Systematic clinical evidence review of NASHA (Durolane hyaluronic acid) for the treatment of knee osteoarthritis. <i>Open Access Rheumatol</i> . 2018;10:43-54. doi: 10.2147/OARRR.S162127.

Claim	• DUROLANE is safe for repeated courses of therapy. Repeated use of DUROLANE does not increase the incidence of adverse events.^{1,2}
Reference	1. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019. 2. Leighton R, Åkermark C, Therrien R, et al. NASHA hyaluronic acid vs methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009

Claim	• During a pivotal trial: - o No serious adverse events were considered related to DUROLANE treatment.¹ - o The most common adverse events were arthralgia (8.6%), injection site pain (2.3%), and joint swelling (1.7%).^{1,2} • In a pivotal trial: - o No serious AEs were considered related to DUROLANE treatment.¹ - o No treatment-related adverse events were seen in 87% of DUROLANE-treated patients.¹
Reference	1. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. <i>Arthritis Res Ther</i>. 2015;17:51. doi:10.1186/s13075-015-0557-x 2. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2019.

Claim	DUROLANE Safety • Available worldwide since 2001, with a low post-market adverse event rate.¹ • A history of safe use^{1,2} • DUROLANE has been evaluated in ten Level 1 clinical studies on OA knee pain. All treatment-related adverse events were local and transient, and most were mild.³⁻¹²
Reference	1. Bioventus LLC. 2021 DUROLANE Post-Market Surveillance (PMS) Review. Data on file, RPT-001411. September 28, 2021 2. Leighton R, Åkermark C, Therrien R, et al. NASHA hyaluronic acid vs methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. <i>Osteoarthritis Cartilage</i>. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009 3. Matas J, Orrego M, Amenabar D, et al. Umbilical cord-derived mesenchymal stromal cells (MSCs) for knee osteoarthritis: repeated MSC dosing is superior to a single MSC dose and to hyaluronic acid in a controlled randomized phase I/II trial. <i>Stem Cells Transl Med</i>. 2019;8(3):215-24. doi:10.1002/sctm.18-0053 4. Buendía-López D, Medina-Quirós M, Fernández-Villacañas Marin MÁ. Clinical and radiographic comparison of a single LP-PRP injection, a single

- hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: a randomized controlled trial. *J Orthop Traumatol.* 2018;19(1):3. doi:10.1186/s10195-018-0501-3
5. Louis ML, Magalon J, Jouve E, et al. Growth factors levels determine efficacy of platelets rich plasma injection in knee osteoarthritis: a randomized double blind noninferiority trial compared with viscosupplementation. *Arthroscopy.* 2018;34(5):1530-40.e2. doi:10.1016/j.arthro.2017.11.035
 6. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. *Arthritis Res Ther.* 2015;17:51. doi:10.1186/s13075-015-0557-x
 7. Vega A, Martín-Ferrero MA, Del Canto F, et al. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. *Transplantation.* 2015;99(8):1681-90. doi:10.1097/TP.0000000000000678
 8. Arden NK, Åkermark C, Andersson M, Todman MG, Altman RD. A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis. *Curr Med Res Opin.* 2014;30(2):279-86. doi:10.1185/03007995.2013.855631
 9. Leighton R, Åkermark C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. *Osteoarthritis Cartilage.* 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009
 10. Vaquerizo V, Plasencia MÁ, Arribas I, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trial. *Arthroscopy.* 2013;29(10):1635-43. doi:10.1016/j.arthro.2013.07.264
 11. Skwara A, Ponelis R, Tibesku CO, Rosenbaum D, Fuchs-Winkelmann S. Gait patterns after intraarticular treatment of patients with osteoarthritis of the knee--hyaluronan versus triamcinolone: a prospective, randomized, double-blind, monocentric study. *Eur J Med Res.* 2009;14(4):157-164. doi:10.1186/2047-783x-14-4-157
 12. Altman RD, Åkermark C, Beaulieu AD, Schnitzer T, Durolane International Study G. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. *Osteoarthritis Cartilage.* 2004;12(8):642-9. doi:10.1016/j.joca.2004.04.010

10. DUROLANE Writing Guidelines

1	<u>Name Usage</u> In all text usage, DUROLANE should be written in all capital letters and is never abbreviated. Bioventus In all text usage, the company name should always begin with a capital B and lowercase the remaining letters. Do not write the name in all caps or in all lower case. The only time the company name should appear in all lower case is within the logo, and it must then be accompanied by the BioSphere. Do not put a trademark symbol beside the company name in text. The word “Bioventus” is never abbreviated. (Do NOT use “BV”, “Biov.”, etc.)
2	<u>Trademark Usage</u> DUROLANE® The first reference OR the most prominent reference of DUROLANE within a document should be appropriately trademarked with the ® symbol (superscripted). Additional uses of the product name do not need the registered trademark symbol. At the end of the document (or for a slide deck, on the slide containing the ®), insert the following trademark notification: DUROLANE is a registered trademark of Bioventus LLC. For competitor products use the following verbiage: "All other trademarks are the property of their respective owners."
3	<u>Bioventus Trademark Usage</u> The Bioventus trademark notification must be on each marketing piece. For non-European countries, use either: • The Bioventus logo is a trademark of Bioventus LLC. • Bioventus and the Bioventus logo are trademarks of Bioventus LLC. • Bioventus, the Bioventus and the DUROLANE logo are registered trademarks of Bioventus LLC.
4	<u>DUROLANE URL</u> www.DUROLANE.com

11. DUROLANE REFERENCE LIST

References must be used exactly as listed in this document.

References are written according to American Medical Association (AMA) citation style (see Appendix 1).

APPENDIX 1. AMERICAN MEDICAL ASSOCIATION (AMA) CITATION STYLE

- Each reference is numbered, and the superscript number in the text is used to indicate the reference
- Superscript numbers are placed outside all punctuation (periods, commas, colons, and semicolons).
- Use commas to separate multiple citation numbers in text
- References are listed numerically in the order they are cited in the text
- Unpublished works and personal communications should be cited in the text (and not on the reference list).
- When citing the same source more than once, give the number of the original reference, and then include the page number (in parentheses) where the information was found.
- For the reference:
 - Include up to 6 authors
 - For more than six authors, provide the names of the first three authors and then add et al
 - If there is no author, start with the title

Citation Type	Example
Journal article – in print – one author	Spencer J. Physician, heal thyself – but not on your own please. <i>Med Educ.</i> 2005;89:548-9.
Journal article – in print – 2-6 authors	Salwachter AR, Freischlag JA, Sawyer RG, Sanfey HA. The training needs and priorities of male and female surgeons and their trainees. <i>J Am Coll Surg.</i> 2005;201:199-205.
Journal article – online *if there is no DOI, provide the URL for the specific article	Coppinger T, Jeanes YM, Hardwick J, Reeves S. Body mass, frequency of eating and breakfast consumption in 9-13-year-olds. <i>J Hum Nutr Diet.</i> 2012;25(1):43-9. doi:10.1111/j.1365-277X.2011.01184.x
Journal article – online from a library database	Calhoun D, Trimarco T, Meek R, Locasto D. Distinguishing diabetes: differentiate between type 1 & type 2 DM. <i>JEMS</i> [serial online]. November 2011; 36(11):32-48. Available from: CINAHL Plus with Full Text, Ipswich, MA. Accessed February 2,

	2012.
Newspaper article – in print *if the city name is not part of the newspaper name, it may be added to the official name for clarity *if an article jumps from one page to a later page write the page numbers like D1, D5	Wolf W. State's mail-order drug plan launched. Minneapolis Star Tribune. May 14, 2004:1B.

Citation Type	Example
Newspaper article – online	Pollack A. FDA approves new cystic fibrosis drug. <i>New York Times</i>. January 31, 2012. Accessed February 1, 2012. https://www.nytimes.com/2012/02/01/business/fda-approves-cystic-fibrosis-drug.html
Websites	Outbreak notice: Cholera in Haiti. Centers for Disease Control and Prevention Web site. Published October 22, 2010. Updated January 9, 2012. Accessed February 1, 2012. wwwnc.cdc.gov/travel/notices/outbreak-notice/haiti-cholera.htm
Entire book – in print	Modlin J, Jenkins P. <i>Decision Analysis in Planning for a Polio Outbreak in the United States</i>. San Francisco, CA: Pediatric Academic Societies; 2004.
Book chapter – in print	Solensky R. Drug allergy: desensitization and treatment of reactions to antibiotics and aspirin. In: Lockey P, ed. <i>Allergens and Allergen Immunotherapy</i>. 3rd ed. Marcel Dekker; 2004:585-606.
Unpublished items presented at a meeting (Includes conferences, oral, and poster presentations)	Durbin D, Kallan M, Elliott M. Risk of injury to restrained children from passenger air bags. Paper presented at: 46th Annual Meeting of the Association for the Advancement of Automotive Medicine; September 2002; Tempe, AZ.

Document Detail

7/29/2022

1

Type: Specifications

Document No.: SPC-000121[B]

Title: DUROLANE Claims Book - US

Owner: MONICA.RAI Monica Rai

Status: RELEASED

Effective Date: 29-Jul-2022

Expiration Date: 29-Jul-2025

Reference

<u>Document No.</u>	<u>Content Type</u>	<u>Relation</u>	<u>Fixed Rev</u>	<u>Status</u>
0059335 [A]	DOCUMENT	Related	No	RELEASED
Title: Dissemination of Promotional Material				
WIN-000266 [B]	DOCUMENT	Related	No	RELEASED
Title: How to set up and review Promotional Materials in PleaseReview				
Q105007-BC [E]	DOCUMENT	Related	No	RELEASED
Title: Legal, Medical, and Regulatory (LMR) Approval Process				

Revision Notes

<u>Document Build No.</u>	<u>Access Activity</u>	<u>Accessed By</u>	<u>Accessed Date</u>
1	Check In	MONICA.RAI	19-Jul-2022
Note:			
2	Check In	MONICA.RAI	20-Jul-2022
Note: The title of Q105007-BC has been updated in Section 3.2.			
3	Check In	MONICA.RAI	20-Jul-2022
Note: The title of Q105007-BC has been updated in Section 3.2.			
4	Check In	MONICA.RAI	20-Jul-2022
Note: The title of Q105007-BC has been updated in Section 3.2.			
5	Check In	MONICA.RAI	25-Jul-2022
Note: Minor update was made to correct the title of Q105007-BC as this was missed in the redline document on the change order.			
6	Check In	MONICA.RAI	25-Jul-2022
Note: Minor update made to correct the title of Q105007-BC. This was missed in the redline document on the change order.			
7	Check In	MONICA.RAI	25-Jul-2022
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8	Check In	MONICA.RAI	25-Jul-2022
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Review

Build No.: 8

Closed Date: 7/29/2022 2:36:06PM

Review: Standard Release Review

Review Purpose: This Review verifies all basic documents and has the typical reviewers attached.

Review Note: SYSTEM AUTO CLOSE REVIEW

Level	Owner Role	Actor	Sign-off Date	Sign-off By
0	BV Configuration Analyst BV Configuration Analyst	AMBER.PLOTNER Amber Plotner	27-Jul-2022 4:30 pm	AMBER.PLOTNER

Note To Reviewer:

Note From Reviewer:Approved as CA

1	BV Doc Owner / Author BV Doc Owner / Author	MONICA.RAI Monica Rai	27-Jul-2022 4:54 pm	MONICA.RAI
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Note To Reviewer:

Note From Reviewer:Approved as document owner

1	BV Doc Approver BV Doc Approver	LIZZIE.FIELDS Lizzie Fields	27-Jul-2022 8:32 pm	LIZZIE.FIELDS
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Note From Reviewer:APPROVED BY RA

1	BV Doc Approver BV Doc Approver	HELEN.SMITH Helen Smith	29-Jul-2022 11:45 am	HELEN.SMITH
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Note From Reviewer:Approved by medical affairs (helen smith)

1	BV Doc Approver BV Doc Approver	TOM.BRADY Thomas C Brady	27-Jul-2022 6:39 pm	TOM.BRADY
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Note From Reviewer:approved, legal, tom brady

2	BV Configuration Analyst BV Configuration Analyst	AMBER.PLOTNER Amber Plotner	29-Jul-2022 2:36 pm	AMBER.PLOTNER
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Note To Reviewer:

Note From Reviewer:Approved as CA