SPECIFICATION: SPC-000068-C

Title: DUROLANE® International Claims Book

Nondisclosure Statement

TABLE OF CONTENTS

1. INTRODUCTION

The purpose of the DUROLANE International Claims Book is to provide all pertinent information for the DUROLANE brand to assist in developing, reviewing, and approving DUROLANE marketing materials. This claims book contains approved messaging, claims supported with references, plus branding and writing information for use OUTSIDE of the U.S.A. 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

DUROLANE is marketed by Bioventus Coöperatief U.A. in different international markets. This specification applies to the European Union (EU), United Kingdom (UK), Ireland, Turkey, Norway, and Switzerland markets' registered indication statement; specific claims can be used in other markets' registered indication statements such as (see chapter 6.1):

- Australia
- Brazil
- Canada
- Chile
- Colombia
- Egypt
- India
- Indonesia
- Jordan
- Malaysia
- Mexico
- Morocco
- New Zealand
- Russia
- Taiwan
- UAE

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

SOR/98-282	The Canadian Medical Device Regulation
2017/745 and 93/42/EEC, as amended by 2007/47/EC	The EU Medical Device Regulation and Medical Device Directive

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
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
TKR	Total knee replacement
TRAE	Treatment-related adverse event

6. REQUIREMENTS

DUROLANE indication 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 exact wording for the registered indication
- The precise claims that can be made

ATTENTION:

Claims must require indication/reference adjustment based on region.

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

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 footnoted throughout the document.

- 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 Indications of Use Based on Territory

Territory of Distribution	Indication statement
EU, Turkey, Switzerland, Norway	**Summary of Indications for Use** **DUROLANE**: Symptomatic treatment of mild to moderate knee or hip osteoarthritis. In addition, DUROLANE has been approved in the EU for the symptomatic treatment associated with mild to moderate osteoarthritis pain in the ankle, shoulder, elbow, wrist, fingers, and toes. DUROLANE is also indicated for pain following joint arthroscopy in the presence of osteoarthritis within 3 months of the procedure. There are no known contraindications. DUROLANE should not be used in patients who have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women. Risks can include transient pain, swelling and/or stiffness at the injection site. Full prescribing information can be found in product labeling, or at www.durolane.com.
Canada	**Summary of Indications for Use** **DUROLANE:** Symptomatic treatment of mild to moderate knee or hip osteoarthritis. In addition, DUROLANE has been approved for the symptomatic treatment associated with mild to moderate osteoarthritis pain in the ankle, fingers, and toes. DUROLANE is also indicated for pain following joint arthroscopy in the presence of osteoarthritis within 3 months of the procedure. Full prescribing information can be found in product labeling, or at

	www.durolane.com.
Australia	**Summary of Indications for Use** **DUROLANE**: Symptomatic treatment of mild to moderate knee or hip osteoarthritis. In addition, DUROLANE has been approved for the symptomatic treatment associated with mild to moderate osteoarthritis pain in the ankle, shoulder, elbow, wrist, fingers, and toes. DUROLANE is also indicated for pain following joint arthroscopy in the presence of osteoarthritis within 3 months of the procedure. DUROLANE is contraindicated in patients with known sensitivity to hyaluronic acid based products. DUROLANE should not be used in patients who have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women. Risks can include transient pain, swelling and/or stiffness at the injection site. Full prescribing information can be found in product labeling, or at www.durolane.com.
UAE, Indonesia, Jordan, Colombia	**Summary of Indications for Use** **DUROLANE:** Symptomatic treatment of mild to moderate knee or hip osteoarthritis. There are no known contraindications. DUROLANE should not be used in patients who have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women. Risks can include transient pain, swelling and/or stiffness at the injection site. Full prescribing information can be found in product labeling, or at www.durolane.com.
New Zealand	**Summary of Indications for Use** **DUROLANE**: Symptomatic treatment associated with mild to moderate osteoarthritis pain in the knee, hip, shoulder, ankle, elbow, wrist, fingers, and toes. DUROLANE is also indicated for pain following joint arthroscopy in the presence of osteoarthritis within 3 months of the procedure. DUROLANE is contraindicated in patients with known sensitivity to hyaluronic acid based products. DUROLANE should not be used in patients who have infections or skin

	disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women. Risks can include transient pain, swelling and/or stiffness at the injection site. Full prescribing information can be found in product labeling, or at www.durolane.com.
Chile	**DUROLANE:** Symptomatic treatment of mild to moderate knee or hip osteoarthritis. There are no known contraindications. You should not use DUROLANE if you have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women. Risks can include transient pain, swelling and/or stiffness at the injection site. Full prescribing information can be found in product labeling, or at www.durolane.com.
India	**Summary of Indications for Use** **DUROLANE:** Symptomatic treatment of mild to moderate knee or hip osteoarthritis. There are no known contraindications. You should not use DUROLANE if you have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women. Risks can include transient pain, swelling and/or stiffness at the injection site. Full prescribing information can be found in product labeling, or at www.durolane.com.
Mexico	**Summary of Indications for Use** **DUROLANE**: Symptomatic treatment of mild to moderate knee osteoarthritis. There are no known contraindications. You should not use DUROLANE if you have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women. Risks can include transient pain, swelling and/or stiffness at the injection site. Full prescribing information can be found in product labeling, or at www.durolane.com.
	Summary of Indications for Use **DUROLANE:** Symptomatic treatment of mild to moderate knee or hip

Russia	osteoarthritis. There are no known contraindications. DUROLANE should not be used if patients have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women. Risks can include transient pain, swelling and/or stiffness at the injection site. Full prescribing information can be found in product labeling, or at www.durolane.com.
Taiwan	**Summary of Indications for Use** **DUROLANE:** Treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, e.g., acetaminophen. Full prescribing information can be found in product labeling, or at www.durolane.com.
Brazil	**Summary of Indications for Use** **DUROLANE:** Symptomatic treatment of mild to moderate knee or hip osteoarthritis. It should be injected by an authorized physician, or in accordance with local legislation. There are no known contraindications. DUROLANE should not be injected if the synovial joint is infected or severely inflamed. DUROLANE should not be injected if there is an active skin disease or infection present at or near the injection site. DUROLANE should not be injected intravascularly or extra-articularly or in the synovial tissues or capsule. Full prescribing information can be found in product labeling, or at www.durolane.com.
Egypt, Morocco, Malaysia, Argentina	**DUROLANE:** Symptomatic treatment of mild to moderate knee or hip osteoarthritis. There are no known contraindications. You should not use DUROLANE if you have infections or skin disease at the injection site. DUROLANE has not been tested in children or pregnant or lactating women. Risks can include transient pain, swelling and/or stiffness at the injection site. Full prescribing information can be found in product labeling, or at www.durolane.com.

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. *Osteoarthritis Cartilage.* 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 relief.[1-5*] **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; 2020. 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. *Osteoarthritis Cartilage.* 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. *J Arthritis.* 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. *Arthritis Res Ther.* 2015;17:51(1). doi:10.1186/s13075-015-0557-x <u>*Add Reference for Taiwan Only:</u> 5. Carney G, Harrison A, Fitzpatrick J. Long-term outcome measures of repeated non-animal stabilized hyaluronic acid (Durolane) injections in

	osteoarthritis: a 6-year cohort study with 623 consecutive patients. *Open Access Rheumatol.* 2021;13:285-92. doi:10.2147/OARRR.S331562

Claim	• Long lasting by design[1-3] **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. *BioDrugs.* 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. *Cartilage.* 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. *Clin Pharmacokinet.* 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[1-3] • 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.
Reference	1. Ågerup B, Berg P, Åkermark C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. *BioDrugs.* 2005;19(1):23-30. doi: 10.2165/00063030-200519010-00003 2. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020. 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. *J Arthritis.* 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. *Osteoarthritis Cartilage.* 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. *Arthritis Res Ther.* 2015;17:51(1).

	doi:10.1186/s13075-015-0557-x

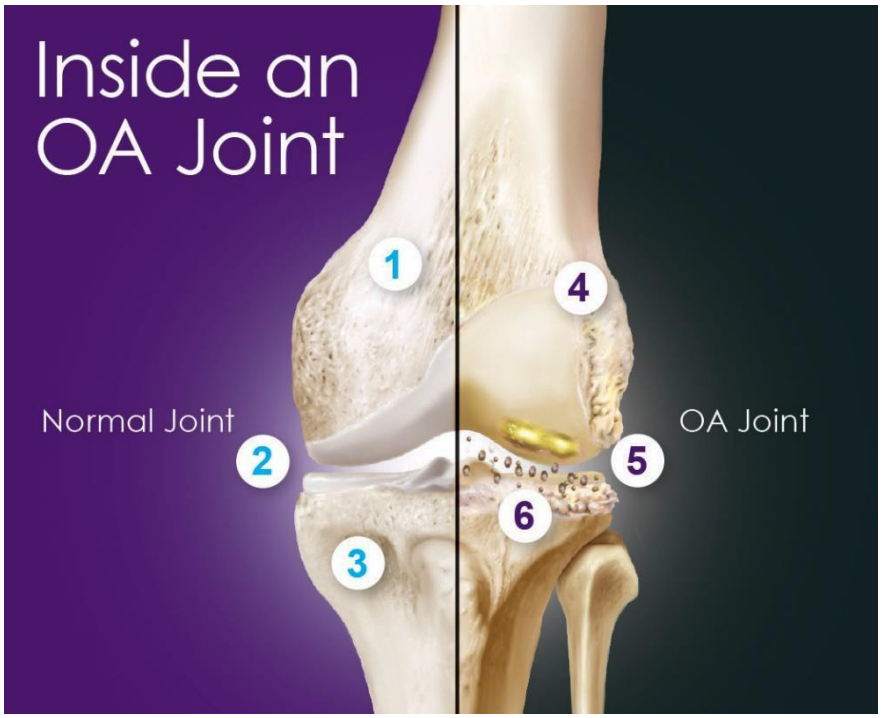
7.2 Messaging for Patients

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

Claim	● 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. *BioDrugs.* 2005;19(1):23-30. doi:10.2165/00063030-200519010-00003 2. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020. 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. *J Arthritis.* 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. *Osteoarthritis Cartilage.* 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. *Arthritis Res Ther.* 2015;17(1):51. doi:10.1186/s13075-015-0557-x

Claim (Patient)	● How do I know if I have OA? o Only a doctor can diagnose you, but there are four important warning signs that mean you should talk to your healthcare provider:[1] 1. Joint pain – The pain may be constant or it may come and go. Pain may occur while at rest or while moving. 2. Joint 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. 3. Joint 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. 4. Difficulty moving a joint – You should not have difficulty or pain when moving a 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? Accessed June 24, 2022. www.arthritis.org/health-wellness/about-arthritis/understanding-arthritis/do-i-have-arthritis

Claim	● What is osteoarthritis (OA)? o 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)? o HA is 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]

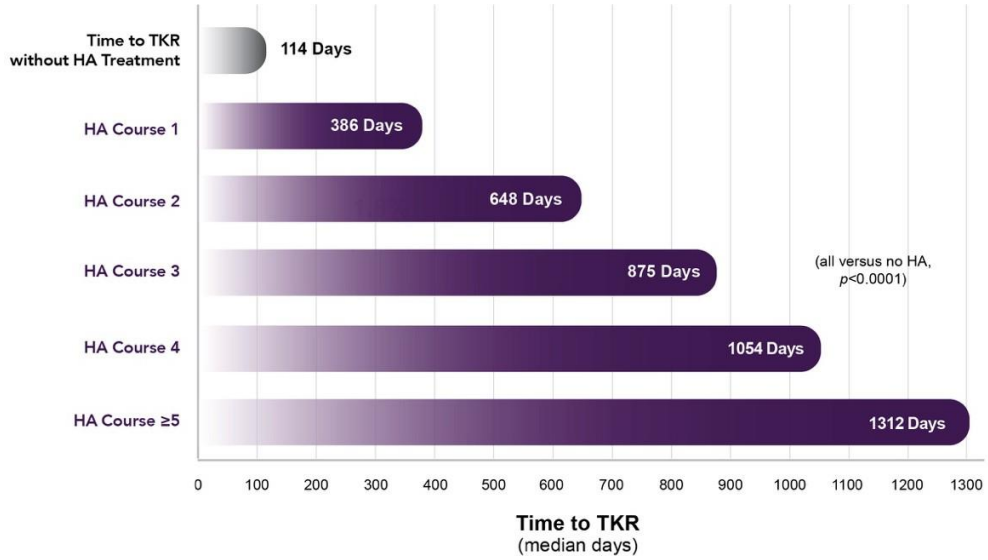
Graphic (Patient)	 1. Normal cartilage: Provides a smooth surface, allowing bones to move easily across each other[3,4] 2. Synovial fluid: Lubricates and provides shock absorption during activity due to a high concentration of HA[3,5] 3. Normal bone: Provides strength and support for the body's tissues[6] 4. Eroded cartilage: If completely worn away, bones may scrape painfully against each other[1] 5. OA synovial fluid: The osteoarthritis disease leads to reduced production of HA, and HA of poor quality[5,7] 6. OA bone: Bony spur growths (osteophytes)[6]
Reference	1. Hsu H, Siwiec RM. Knee osteoarthritis. Last updated April 30, 2022. www.ncbi.nlm.nih.gov/books/NBK507884/ 2. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020. 3. Tamer TM. Hyaluronan and synovial joint: function, distribution and healing. *Interdiscip Toxicol*. 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. *J Exp Orthop.* 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. *J Pain Res.* 2018;11:2189-96. doi:10.2147/JPR.S154002 6. Clarke B. Normal bone anatomy and physiology. *Clin J Am Soc Nephrol.* 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. *Adv Mater*. 2019;31(46):e1904535. doi:10.1002/adma.201904535

Claim	● HA in your joints is continuously broken down and replaced over time.[1] o 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] o The pain caused by inflammation limits movement,[3,4] which in turn can lead to further deterioration of the joint.[5]
Reference	1. Li H, Guo H, Lei C, et al. Nanotherapy in joints: increasing endogenous hyaluronan production by delivering hyaluronan synthase 2. *Adv Mater*. 2019;31(46):e1904535. doi:10.1002/adma.201904535 2. Mora JC, Przkora R, Cruz-Almeida Y. Knee osteoarthritis: pathophysiology and current treatment modalities. *J Pain Res.* 2018;11:2189-96. doi:10.2147/JPR.S154002 3. 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. *BMC Musculoskelet Disord*. 2015;16:321. doi:10.1186/s12891-015-0775-z 4. Mease PJ, Hanna S, Frakes EP, Altman RD. Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. *J Rheumatol.* 2011;38(8):1546-51. doi:10.3899/jrheum.100759 5. Brody LT. Knee osteoarthritis: clinical connections to articular cartilage structure and function. *Phys Ther Sport.* 2015;16(4):301-16. doi:10.1016/j.ptsp.2014.12.001 6. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020.

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 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 may help delay the need for knee replacement surgery.*[1] ● Repeated injections of HA therapy may delay the need for knee replacement surgery.*[1] *Add Footnote: *The study by Altman et al. 2015 does not contain data specific to DUROLANE.*

Graphic* [Altman 2015: 6a/Table3]	
Reference	1. 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 2. Romero Jurado M, Enrique Fidalgo A, Rodríquez Villar V, Mar Medina J, Soler López B. Factors related with the time to surgery in waiting-list patients for knee prostheses. *Reumatol Clin.* 2013;9(3):148-55. doi:10.1016/j.reuma.2012.09.003

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

Claim	• HMW HA > 3000 kDa were reported to improve clinical outcomes.[1*]
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. *Cartilage.* 2019;10(1):43-52. doi:10.1177/1947603517749919 *Add Footnote: *The study by Altman et al. 2015 does not contain data specific to DUROLANE.*

Claim	• Did you know HA injections: o Can relieve OA knee pain for 6 months[1] o May delay the need for knee replacement surgery[2*,3] o Are a natural, non-opioid therapy?[4] *Add Footnote: *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. *Arthritis Res Ther*. 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. *PLoS One.* 2015;10(12):e0145776. doi:10.1371/journal.pone.0145776 3. Romero Jurado M, Enrique Fidalgo A, Rodríguez Villar V, Mar Medina J, Soler López B. Factors related with the time to surgery in waiting-list patients for knee prostheses. *Reumatol Clin.* 2013;9(3):148-55. doi:10.1016/j.reuma.2012.09.003 4. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020.

Claim	• HA treatments can provide 6-12 months of OA pain relief with minimal risk of complications.[1-8*] • HA can provide 6-12 months of OA knee pain relief.[1-8*]
Reference	1. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020. 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. *Arthritis Res Ther.* 2015;17(1):51. doi:10.1186/s13075-015-0557-x 3. 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 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. *Arthritis Rheum.* 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. *J Arthritis.* 2013;2(1):108. doi:10.4172/2167-7921.1000108 6. Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. *Z Rheumatol*. 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. *J Rheumatol Suppl*. 1993;39:3-9. <u>*Add Reference for Taiwan Only:</u> 8. Carney G, Harrison A, Fitzpatrick J. Long-term outcome measures of repeated non-animal stabilized hyaluronic acid (Durolane) injections in osteoarthritis: a 6-year cohort study with 623 consecutive patients*. Open Access Rheumatol*. 2021;13:285-92. doi:10.2147/OARRR.S331562

8.1 Alternative Treatment Options for OA

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

8.1.1 Opioids

Claim	● Opioids are associated with faster progression of degenerative changes in knee osteoarthritis.[1] ● Prescription rates for opioids to treat knee OA pain remain significant in the United States, at nearly 16% of patients with knee OA prescribed an opioid for their condition.[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). *Arthritis Res Ther.* 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? *J Arthroplasty*. 2017;32(12):3578-82.e1. doi:10.1016/j.arth.2017.07.030

8.1.2 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) also 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] o A total of 32% of IAC-treated patients experienced Kellgren-Lawrence grade (KL) worsening after 1 year versus 15% of a comparison cohort without IAC treatment.[2] ● HA has been proven to provide 6-12 months of pain relief—much longer than steroids.[3-5*]
Reference	1. 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. *JAMA*. 2017;317(19):1967-75. doi:10.1001/jama.2017.5283 2. Zeng C, Lane NE, Hunter DJ, et al. Intra-articular corticosteroids and the risk of knee osteoarthritis progression: results from the Osteoarthritis Initiative. *Osteoarthritis Cartilage.* 2019;27(6):855-62. doi:10.1016/j.joca.2019.01.007 3. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020. 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. *Osteoarthritis Cartilage*. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009 <u>*Add Reference for Taiwan Only:</u> 5. Carney G, Harrison A, Fitzpatrick J. Long-term outcome measures of repeated non-animal stabilized hyaluronic acid (Durolane) injections in osteoarthritis: a 6-year cohort study with 623 consecutive patients. *Open Access Rheumatol.* 2021;13:285-92. doi:10.2147/OARRR.S331562

8.1.3 Platelet-Rich Plasma

Claim	● Studies have shown mixed results with respect to the effectiveness of platelet-rich plasma (PRP) in treating OA.[1] o 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, current clinical guidelines recommend strongly against the use of PRP to treat OA.[1,2]
Reference	1. Ding JB, Hu K. Injectable therapies for knee osteoarthritis. *Reumatologia.* 2021;59(5):330-9. doi:10.5114/reum.2021.110612 2. 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. *Arthritis Care Res (Hoboken)*. 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.

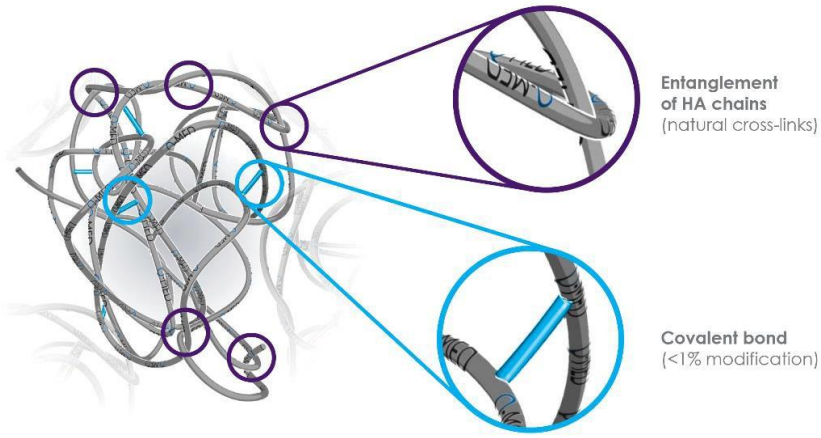
9.1 Product Description/Manufacturing Process

These claims describe DUROLANE and its unique manufacturing process.

Claim	● DUROLANE is available in 3 mL.[1-2] ● DUROLANE is a single-injection course of therapy.[1-2]
Reference	1. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020.

Claim	● DUROLANE contains 20 mg/mL of stabilized hyaluronic acid (NASHA®) in buffered physiologicalsodium chloride solution pH 7.[1-2]
Reference	1. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020.

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]

Graphic	 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. *BioDrugs.* 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. *Cartilage.* 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. *Clin Pharmacokinet.* 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.[1] ● The highest reported molecular weight HA product.[1,2] ● DUROLANE has a molecular weight of 10^{15} kDa.[1] ● 10^{15} kDa Molecular Weight.[1]
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. *Clin Med Insights Arthritis Musculoskelet Disord*. 2018;11:1179544117751622. doi:10.1177/1179544117751622

Claim	• The molecular weight of DUROLANE can be expressed in the following ways:[1] o 1 000 000 000 000 000 000 Da o 10^{18} Da o 10^{15} kDa o o 10^{12} 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.[2] • Biocompatibility maintained through minimal cross-linking.[1]
Reference	1. Ågerup B, Berg P, Åkermark C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. *BioDrugs*. 2005;19(1):23-30. doi:10.2165/00063030-200519010-00003 2. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020.

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. *J Biomed Mater Res B Appl Biomater.* 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	1. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020. 2. Synvisc-One [package insert]. Ridgeway, NJ: Genzyme Biosurgery; 2014.

Claim	• Comparison chart[1,2]
Graphic	

Comparison chart[1-2]	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	1. Synvisc-One [package insert]. Ridgeway, NJ: Genzyme Biosurgery; 2014. 2. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020.

Claim	• Comparison chart.[1-11]
Graphic	

	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[4,5]	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

Reference	1. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020. 2. Lindqvist U, Tolmachev V, Kairemo K, Åström G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. *Clin Pharmacokinet.* 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004 3. Edsman K, Hjelm R, Lärkner H, et al. Intra-articular duration of Durolane™ after single injection into the rabbit knee. *Cartilage.* 2011;2(4):384-8. doi:10.1177/1947603511400184

4. Bioventus LLC. Q-Med Molecular Weight of DUROLANE. Data on file, RPT-001314. June 2021.
5. Wooley PH, Song Z, Harrison A. Hyaluronic acid viscosupplements from avian and non-mammalian sources exhibit biocompatibility profiles with unique, source-specific, antigenic profiles. *J Biomed Mater Res B Appl Biomater*. 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. *Ann Rheum Dis*. 2010;69(1):113-9. 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. *J Biomed Mater Res B Appl Biomater*. 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. *BMC Musculoskelet Disord*. 2016;17:240. doi:10.1186/s12891-016-1101-0
11. Monovisc [package insert]. Bedford, MA: Anika Therapeutics, Inc.; 2013.

Claim

- Comparison chart of single-injection HA products.[1-7]

Graphic

	DUROLANE[1-3]	Synvisc-One®[4,5]	Monovisc®[6]	Cingal®[6,7]
Molecular weight (Da)	10^{18}	6 M	1-2.9 M	1-2.9 M
NASHA stabilized formulation	✓	x	x	x
Half-life	30 days	1.5-8.8 days	n/a	n/a
Volume/injection	3 mL	6 mL	4 mL	4 mL
HA concentration	20 mg/mL	8 mg/mL	22 mg/mL	22 mg/mL

Da=daltons; HA=hyaluronic acid; n/a=not available.

Reference

1. Bioventus LLC. Q-Med Molecular Weight of DUROLANE. Data on file, RPT-001314. June 2021.
2. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020.
3. Lindqvist U, Tolmachev V, Kairemo K, Åström G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. *Clin Pharmacokinet.* 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004
4. Synvisc-One [package insert]. Ridgeway, NJ: Genzyme Biosurgery; 2014.
5. Larsen NE, Dursema HD, Pollak CT, Skrabut EM. Clearance kinetics of a

	hylan-based viscosupplement after intra-articular and intravenous administration in animal models. *J Biomed Mater Res B Appl Biomater*. 2012;100(2):457-62. doi:10.1002/jbm.b.31971 6. Monovisc [package insert]. Bedford, MA: Anika Therapeutics, Inc.; 2013. 7. Cingal [package insert]. Bedford, MA: Anika Therapeutics, Inc.; 2015.

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. *Cartilage.* 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. *J Biomed Mater Res B Appl Biomater.* 2012;100(2):457-62. doi:10.1002/jbm.b.31971 3. Lindqvist U, Tolmachev V, Kairemo K, Åström G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. *Clin Pharmacokinet.* 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 residencetime in the joint.*[1-3] ***Add Note:** *Preclinical residence time has not been correlated with the duration of clinical effect.*
Reference	1. Ågerup B, Berg P, Åkermark C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. *BioDrugs.* 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. *Cartilage.* 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. *Clin Pharmacokinet.* 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004

Claim	• DUROLANE has a half-life of 32 days in the animal joint following a single injection.[1]
Reference	1. Edsman K, Hjelm R, Lärkner H, et al. Intra-articular duration of Durolane™ after single injection into the rabbit knee. *Cartilage.* 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 with 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. *Clin Pharmacokinet.* 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004

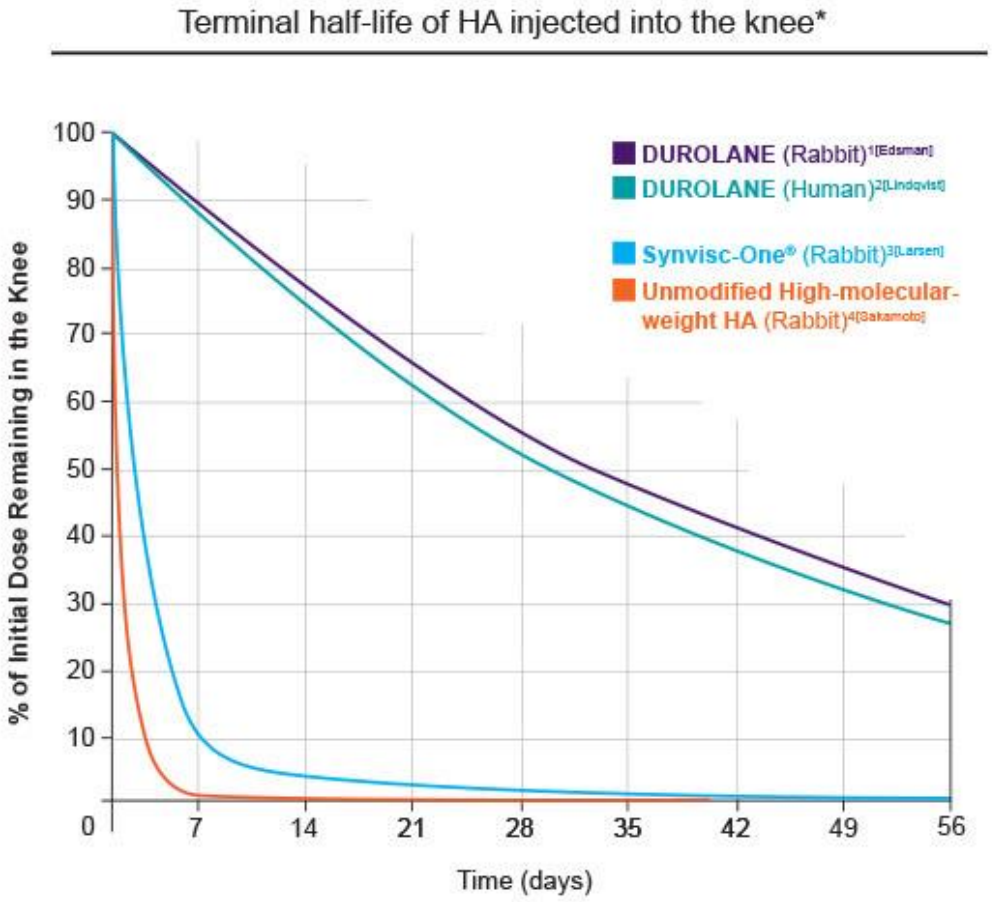
Claim	• DUROLANE has a longer half-life than unstabilized HA.*[1-2] ***Add Note:** *Preclinical residence time has not been correlated with the duration of clinical effect.*
Reference	1. Brown TJ, Laurent UB, Fraser JR. Turnover of hyaluronan in synovial joints: elimination of labelled hyaluronan from the knee joint of the rabbit. *Exp Physiol.*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. *Cartilage.* 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:** *Preclinical residence time has not been correlated with the duration of clinical effect.*
Reference	1. Edsman K, Hjelm R, Lärkner H, et al. Intra-articular duration of Durolane™ after single injection into the rabbit knee. *Cartilage.* 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. *J Biomed Mater Res B Appl Biomater.* 2012;100(2):457-62. doi:10.1002/jbm.b.31971 3. Lindqvist U, Tolmachev V, Kairemo K, Åström G, Jonsson E, Lundqvist H.

	Elimination of stabilised hyaluronan from the knee joint in healthy men. *Clin Pharmacokinet.* 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004

Claim	• DUROLANE has a longer half-life than unstabilized hyaluronic acid (HA)*[1-3] and cross-linked Synvisc-One® (hylan G-F 20).*[2-4] ***Add Note:** *Preclinical residence time has not been correlated with the duration of clinical effect.* **NOTE:** *Each of the two comparisons need to always be associated with their respective reference.*
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. *Exp Physiol.* 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. *Cartilage.* 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. *Clin Pharmacokinet.* 2002;41(8):603-13. doi:10.2165/00003088-200241080-00004 4. Larsen NE, Dursema HD, Pollak CT, Skrabut EM. Clearance kinetics of a hylan- based viscosupplement after intra-articular and intravenous administration in animal models. *J Biomed Mater Res B Appl Biomater*. 2012;100(2):457-62. 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 based on a half-life of 30 days.*[1,2] ***Add Note:** *Preclinical residence time has not been correlated with the duration of clinical effect.*
Reference	1. 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. 2. Lindqvist U, Tolmachev V, Kairemo K, Åström G, Jonsson E, Lundqvist H. Elimination of stabilised hyaluronan from the knee joint in healthy men. *Clin Pharmacokinet.* 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 in 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:** *Preclinical residence time has not been correlated with the duration of clinical effect.*
Graph [Edsman 2011: 4a; Lindqvist 2002: 1a-b; Larsen 2012: 1a; Sakamoto 1984: 1a,5a]	
Reference	1. Edsman K, Hjelm R, Lärkner H, et al. Intra-articular duration of Durolane™ after single injection into the rabbit knee. *Cartilage.* 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. *Clin Pharmacokinet.* 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. *J Biomed Mater Res B Appl Biomater*. 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. *Pharmacometrics*. 1984;28(2):375-87.

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 syringes[1,2] ● 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; 2020.

Claim	● DUROLANE was designed as a single-injection course of therapy.[1]
Reference	1. Ågerup B, Berg P, Åkermark C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. *BioDrugs.* 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.[1]
Reference	1. Bioventus. Data on File. RPT-001367. Accessed June 2022.

Claim	● DUROLANE is a single-injection HA designed to deliver powerful, long-lasting osteoarthritis (OA) knee pain relief.[1-7*] ● DUROLANE is a one-injection HA treatment designed to deliver powerful, long-lasting knee OA pain relief.[1-7*] ● DUROLANE was designed as a single-injection treatment for convenient, long-lasting treatment.[1-7*] ● Help 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.[1-7*] **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. *J Arthritis.* 2013;2(1):1000108. doi:10.4172/2167-7921.1000108 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. *Osteoarthritis Cartilage*. 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. *Arthritis Res Ther*. 2015;17(1):51. doi:10.1186/s13075-015-0557-x 4. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020. 5. Ågerup B, Berg P, Åkermark C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. *BioDrugs*. 2005;19(1):23-30. doi: 10.2165/00063030-200519010-00003 6. Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. *Z Rheumatol*. 2006;65(4):327-31. doi: 10.1007/s00393-006-0063-2. <u>*Add Reference for Taiwan Only:</u> 7. Carney G, Harrison A, Fitzpatrick J. Long-Term Outcome Measures of Repeated Non-Animal Stabilized Hyaluronic Acid (Durolane) Injections in Osteoarthritis: A 6-Year Cohort Study with 623 Consecutive Patients. *Open Access Rheumatol.* 2021;13:285-292. doi: 10.2147/OARRR.S331562.

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 indicated joint pain due to OA.[1-5] ● What are the benefits of DUROLANE? o DUROLANE reduces knee joint pain for up to 6-12 months and improves physical activity and quality of life of knee OA patients in as early as 2 weeks, for up to 24 weeks.[1-6*] ● 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 right for you.[1] Speak with your doctor about HA treatment with DUROLANE. ● Is there any reason why I couldn't have a DUROLANE injection? o 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.[1] o 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.[1]

Reference	1. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020. 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. *Osteoarthritis Cartilage*. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009 3. 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. *Arthritis Rheum*. 2009;61(12):1704-11. doi:10.1002/art.24925 4. 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. *J Arthritis*. 2013;2(1):1000108. doi:10.4172/2167-7921.1000108 5. Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. *Z Rheumatol*. 2006;65(4):327-31. doi:10.1007/s00393-006-0063-2 <u>*Add Reference for Taiwan Only:</u> 6. Carney G, Harrison A, Fitzpatrick J. Long-Term Outcome Measures of Repeated Non-Animal Stabilized Hyaluronic Acid (Durolane) Injections in Osteoarthritis: A 6-Year Cohort Study with 623 Consecutive Patients. Open Access Rheumatol. 2021;13:285-292. doi: 10.2147/OARRR.S331562.

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.[1] ● The primary efficacy variable was the Likert 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	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. *Arthritis Res Ther.* 2015;17(1):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 WOMAC pain scale responder rate at 12 weeks.[1] ● Secondary efficacy variables included change from baseline scores of 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, 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

9.6.2 Equivalence / Non-inferiority

Claim	● DUROLANE is the only single-injection HA proven to be clinically equivalent to a five-injection HA 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] o 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 pain relief at 6 months equivalent 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. *Arthritis Res Ther*. 2015;17(1):51. doi:10.1186/s13075-015-0557-x 2. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020.

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]
	  o 45% of patients treated with DUROLANE experienced pain control for 12 weeks.[1]
	  o This effect was sustained 26 weeks after the initial injection.
	● In a non-inferiority study, one injection of DUROLANE produced clinically equivalent pain relief at 12 weeks equivalent to pain relief achieved with a corticosteroid injection.[1,2]
	  o The benefit of DUROLANE was maintained at 26 weeks, while the

	benefit of the corticosteroid injection declined.
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. *Osteoarthritis Cartilage.* 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[1-6*] o Nearly 8 in 10 patients (79%) experienced improved pain control versus baseline pain 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 versus baseline pain, assessed with the visual analog scale.[1] ● 26 weeks of improved relief from baseline pain in a pivotal, non-inferiority study.[1]
Graphic [Zhang 2015: 7a]	
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. *Arthritis Res Ther.* 2015;17(1):51. doi:10.1186/s13075-015-0557-x 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. *Osteoarthritis Cartilage.* 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. *J Arthritis.* 2013;2(1):1000108. doi:10.4172/2167-7921.1000108 4. Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. *Z Rheumatol*. 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. *Open Access Rheumatol.* 2018;10:43-54. doi:10.2147/OARRR.S162127

	*Add Reference for Taiwan Only: 6. Carney G, Harrison A, Fitzpatrick J. Long-Term Outcome Measures of Repeated Non-Animal Stabilized Hyaluronic Acid (Durolane) Injections in Osteoarthritis: A 6-Year Cohort Study with 623 Consecutive Patients. Open Access Rheumatol. 2021;13:285-292. doi: 10.2147/OARRR.S331562.

Claim	• 93% of DUROLANE-treated patients had a decrease in pain over baseline while walking on a flat surface at week 18.[1]
Graphic [Zhang 2015: 7b]	 *In WOMAC subscores
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. *Arthritis Res Ther.* 2015;17(1):51. doi:10.1186/s13075-015-0557-x

Claim	• Approximately 9 in 10 patients treated with DUROLANE felt reduced pain over baseline walking on a flat surface at week 26.[1] **[Zhang 2015: 7b-c]**
Graphic [Zhang 2015: 7b-c]	
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. *Arthritis Res Ther.* 2015;17(1):51. doi:10.1186/s13075-015-0557-x

Claim	• One injection of DUROLANE provided up to 12 months of pain relief,

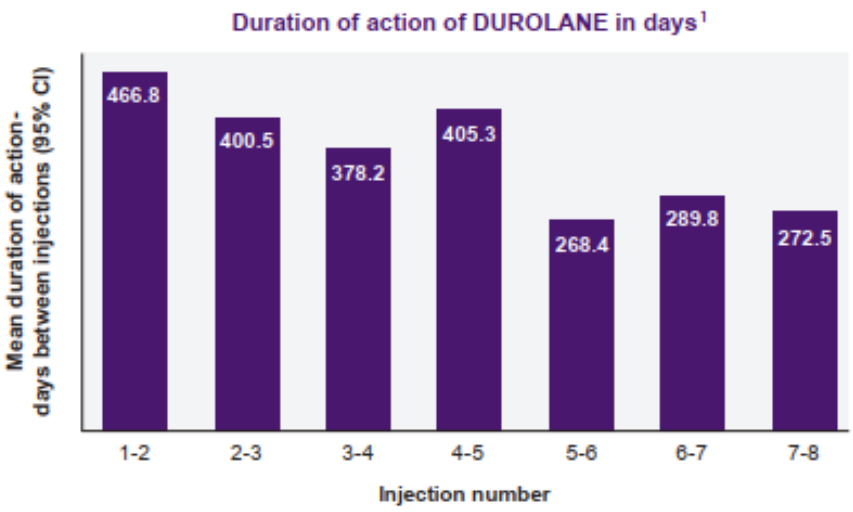
	reducing the need for rescue medications.[1,2*]
Reference	1. Zhang H, Zhang K, Zhang X, et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. *Arthritis Res Ther*. 2015;17(1):51. doi:10.1186/s13075-015-0557-x *Add Reference for Taiwan Only: 2. Carney G, Harrison A, Fitzpatrick J. Long-Term Outcome Measures of Repeated Non-Animal Stabilized Hyaluronic Acid (Durolane) Injections in Osteoarthritis: A 6-Year Cohort Study with 623 Consecutive Patients. *Open Access Rheumatol.* 2021;13:285-292. doi: 10.2147/OARRR.S331562

Claim‡	• DUROLANE offers powerful and lasting pain relief.[1-9*]
Reference	**Knees:** 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. *Osteoarthritis Cartilage.* 2014;22(1):17–25. doi:10.1016/j.joca.2013.10.009 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. *J Arthritis.* 2013; 2(1):1000108. doi:10.4172/2167-7921.1000108 3. Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. *Z Rheumatol.* 2006;65(4):327-31. doi:10.1007/s00393-006-0063-2 4. 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. *Open Access Rheumatol.* 2018;10:43-54. doi:10.2147/OARRR.S162127 **Hip:** 5. Conrozier T, Couris CM, Mathieu P, et al. Safety, efficacy and predictive factors of efficacy of a single intra-articular injection of non-animal-stabilized-hyaluronic-acidin the hip joint: results of a standardized follow-up of patients treated for hip osteoarthritis in daily practice. *Arch Orthop Trauma Surg.* 2009;129(6):843–8. doi:10.1007/s00402-008-0778-4 **Thumb:** 6. Velasco E, Ribera MV, Pi J. Single-arm open-label study of Durolane (NASHA nonanimal hyaluronic acid) for the treatment of osteoarthritis of the thumb. *Open Access Rheumatol*. 2017;9:61-6. doi:10.2147/OARRR.S128675 **Shoulder:** 7. McKee MD, Litchfield R, Hall JA, Wester T, Jones J, Harrison AJ. NASHA

	hyaluronic acid for the treatment of shoulder osteoarthritis: a prospective, single-arm clinical trial. *Med Devices (Auckl).* 2019;12:227-34. doi:10.2147/MDER.S189522 **Ankle:** 8. Younger ASE, Penner M, Wing K, et al. Nonanimal hyaluronic acid for the treatment of ankle osteoarthritis: a prospective, single-arm cohort study. *J Foot Ankle Surg.* 2019;58(3):514-8. doi:10.1053/j.jfas.2018.10.003 <u>*Add Reference for Taiwan Only:</u> **Multi-joint (knee, hip, and shoulder):** 9. Carney G, Harrison A, Fitzpatrick J. Long-term outcome measures of repeated non-animal stabilized hyaluronic acid (Durolane) injections in osteoarthritis: a 6-year cohort study with 623 consecutive patients. Open *Access Rheumatol.* 2021;13:285-92. doi:10.2147/OARRR.S331562

Claim	• DUROLANE has demonstrated efficacy in relieving osteoarthritis pain for at least 12 months.[1*] • The therapeutic effect of a single DUROLANE injection may last longer than 1 year.[1*] • One year of pain relief from a single injection.[1*]
Reference	<u>*Footnote: Use Claims for Taiwan only</u> (*Any claims over 12 months of pain relief should not be used unless you are "showcasing" the Carney study alone. It is not a forward-projecting claim and must be tied to this study specifically*.) 1. Carney G, Harrison A, Fitzpatrick J. Long-term outcome measures of repeated non-animal stabilized hyaluronic acid (Durolane) injections in osteoarthritis: a 6-year cohort study with 623 consecutive patients. *Open Access Rheumatol.* 2021;13:285-92. doi:10.2147/OARRR.S331562

Claim	• Repeat injections are equally durable for 12+ years. [1*] • 4 repeat injections are equally durable for 12+ years. [1*] • Four consecutive injections are equally durable up to 4.5 years.[1*] • Four repeat injections each last longer than 1 year. [1*] • Four consecutive injections each last longer than 1 year. [1*] • Four repeat injections each provide more than 1 year of pain relief. [1*] • Four consecutive injections each provide more than 1 year of pain relief. [1*] Four repeat injections each provide more than 1 year of pain relief; a further 3 consecutive/repeat injections each provide an additional 8 months of pain relief. [1*]

Graph [Carney 2021: 5a]	 Graph of duration of symptom relief in days for each injection. X-axis = number of injections, Y-axis = mean number of days.
Reference	<u>*Footnote: Use Claims for Taiwan only</u> (*Any claims over 12 months of pain relief should not be used unless you are "showcasing" the Carney study alone. It is not a forward-projecting claim and must be tied to this study specifically*.) 1. Carney G, Harrison A, Fitzpatrick J. Long-term outcome measures of repeated non-animal stabilized hyaluronic acid (Durolane) injections in osteoarthritis: a 6-year cohort study with 623 consecutive patients. *Open Access Rheumatol.* 2021;13:285-92. doi:10.2147/OARRR.S331562

Claim	• Osteoarthritis pain relief with DUROLANE can be sustained for at least 12 months post initial treatment.[1]* • Patients who receive subsequent injections of DUROLANE can also experience an extended duration of pain relief. [1]* • Patients with grades 2 or 3 osteoarthritis are more likely to experience a longer duration of pain relief (12+ months) with DUROLANE from a single injection.[1]*
Reference	<u>*Footnote: Use Claims for Taiwan only</u> (*Any claims over 12 months of pain relief should not be used unless you are "showcasing" the Carney study alone. It is not a forward-projecting claim and must be tied to this study specifically*.) 1. Carney G, Harrison A, Fitzpatrick J. Long-term outcome measures of repeated non-animal stabilized hyaluronic acid (Durolane) injections in osteoarthritis: a 6-year cohort study with 623 consecutive patients. *Open Access Rheumatol.* 2021;13:285-92. doi:10.2147/OARRR.S331562

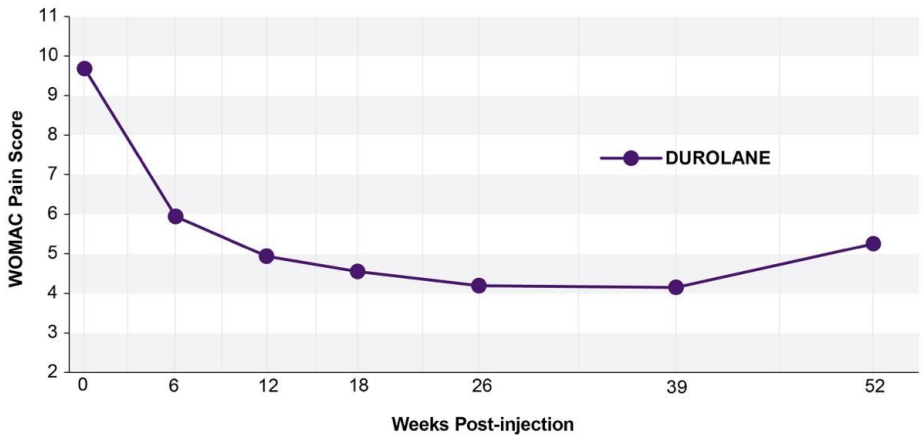
Claim	• 76% of patients treated with DUROLANE for osteoarthritis experienced pain relief, from 6 to 12+ months.[1*] • 65% of the patients would recommend DUROLANE for OA.[1] • After their first injection, 65% of patients felt significant relief from their OA symptoms.[1] • After their second injection, 81% of patients felt significant relief from their OA symptoms.[1]
Reference	*Footnote: For Taiwan only (*Any claims over 12 months of pain relief should not be used unless you are "showcasing" the Carney study alone. It is not a forward-projecting claim and must be tied to this study specifically*.) 1. Carney G, Harrison A, Fitzpatrick J. Long-term outcome measures of repeated non-animal stabilized hyaluronic acid (Durolane) injections in osteoarthritis: a 6-year cohort study with 623 consecutive patients. *Open Access Rheumatol.* 2021;13:285-92. doi:10.2147/OARRR.S331562

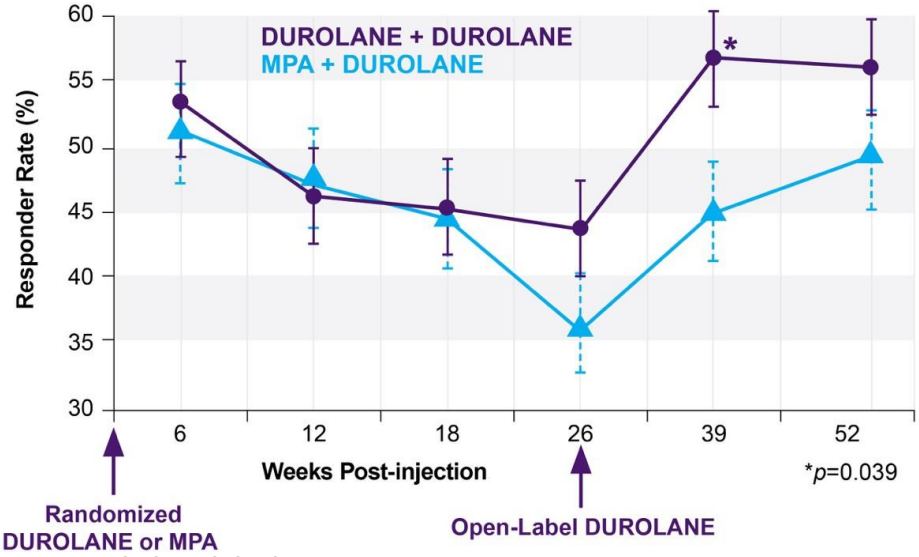
Claim	• When treating mild to moderate osteoarthritis, DUROLANE can provide long-term pain relief.[1*]
Reference	*Footnote: Use Claims for Taiwan only (*Any claims over 12 months of pain relief should not be used unless you are "showcasing" the Carney study alone. It is not a forward-projecting claim and must be tied to this study specifically*.) 1. Carney G, Harrison A, Fitzpatrick J. Long-term outcome measures of repeated non-animal stabilized hyaluronic acid (Durolane) injections in osteoarthritis: a 6-year cohort study with 623 consecutive patients. *Open Access Rheumatol.* 2021;13:285-92. doi:10.2147/OARRR.S331562

Claim	• Preliminary data suggest that a single injection of NASHA may provide 6 months of pain relief for patients with symptomatic glenohumeral osteoarthritis.[1]
Reference	1. McKee MD, Litchfield R, Hall JA, Wester T, Jones J, Harrison AJ. NASHA hyaluronic acid for the treatment of shoulder osteoarthritis: a prospective, single-arm clinical trial. *Med Devices (Auckl).* 2019;12:227-34. doi:10.2147/MDER.S189522

Claim	• A single injection of DUROLANE for the treatment of ankle osteoarthritis is associated with clinically meaningful reductions in pain and disability for up to 26 weeks.[1]
Reference	1. Younger ASE, Penner M, Wing K, Vet al. Nonanimal hyaluronic acid for the treatment of ankle osteoarthritis: a prospective, single-arm cohort study. *J Foot Ankle Surg*. 2019;58(3):514-8. doi:10.1053/j.jfas.2018.10.003

Claim	• DUROLANE is effective and well tolerated in treating the symptoms of thumb osteoarthritis.[1]
Reference	1. Velasco E, Ribera MV, Pi J. Single-arm open-label study of Durolane (NASHA nonanimal hyaluronic acid) for the treatment of osteoarthritis of the thumb. *Open Access Rheumatol*. 2017 Mar 27;9:61-66. doi:10.2147/OARRR.S128675.

Claim	• Long lasting pain relief, for up to 12 months.[1] • Some patients maintained relief from baseline over the 12-month period.[1] • The responder rate was 50% at 1 year.[2] • 31 of 194 patients (16%) from the DUROLANE group did not feel the need for a second IA treatment.[1] **Note:** 12-month claims and reference to 12-month outcomes from Leighton et al, 2014 should only be used on materials specific to Leighton et al. 2014 and not generic marketing pieces.
Graph [RPT-00641: 43a]	
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. *Osteoarthritis Cartilage.* 2014;22(1):17–25. doi:10.1016/j.joca.2013.10.009

	2. Bioventus LLC. MA-12200 Study report, open-label extension study 3, DUROLANE vs MPA. Data on file, RPT-00641.
Claim	• After 6 months, all patients were offered a DUROLANE injection in the open-label phase.[1] • DUROLANE second injection led to higher WOMAC Pain responder rates at 39 and 52 weeks, than at 26 weeks.*[1] • DUROLANE treatment following steroid injection is a viable option.[1] *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: 7b,c]	 MPA: methylprednisolone acetate
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. *Osteoarthritis Cartilage.* 2014;22(1):17–25. doi:10.1016/j.joca.2013.10.009

9.6.4 Improved Function

Claim	• Improved knee function: o Physical function improved 59% at 26 weeks among patients in the DUROLANE treatment group (p<0.0001).[1] o Patient reported physical function improved by 59% at 26 weeks.[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. *Arthritis Res Ther.* 2015;17(1):51. doi:10.1186/s13075-015-0557-x

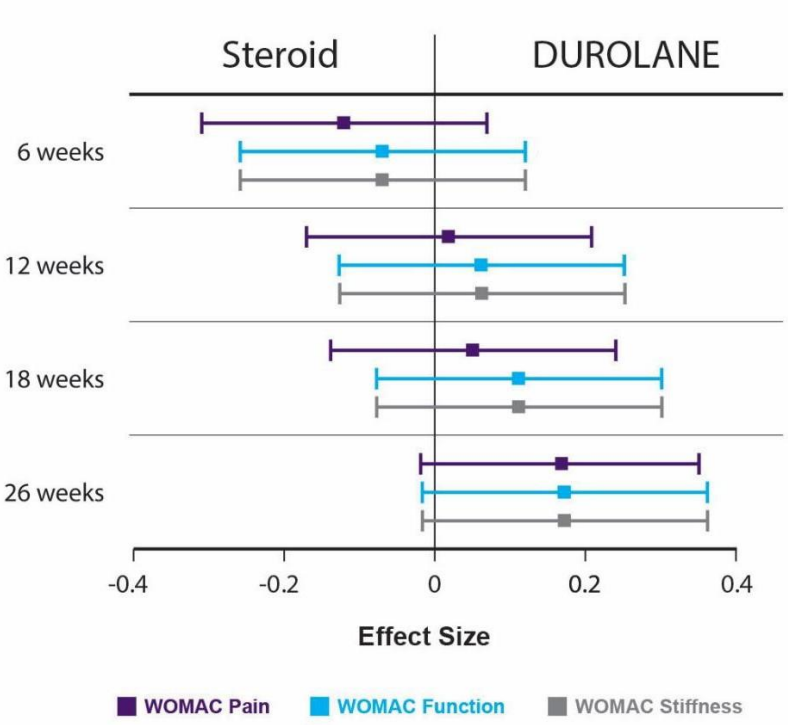
Claim	• Two weeks after a DUROLANE injection, subjective evaluations of knee function that measured activities of daily living and sports/leisure activities improved significantly (p<0.001 for both).[1] • Significant improvement was seen in all Knee Injury and Osteoarthritis Outcome Score (KOOS) parameters,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

9.7 Comparative Studies - Efficacy and Safety

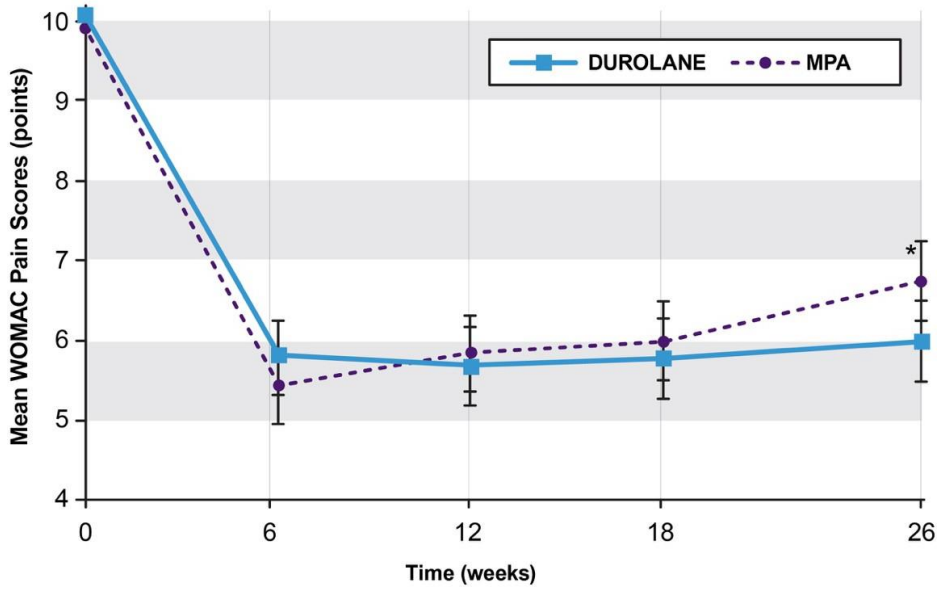
These claims address the comparative efficacy and safety of DUROLANE with other standard of care treatments for OA.

Claim	• In a Level 1 study, the effects of DUROLANE were longer lasting than the steroid MPA, 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] *MPA, methylprednisolone acetate
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. *Osteoarthritis Cartilage.* 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009

Claim	• Longer-lasting knee pain relief versus steroid*[1] • DUROLANE was proven to be noninferior to steroid at 6 weeks.†[1] o Results favored DUROLANE for WOMAC pain, function, and stiffness scores from 12 to 26 weeks.[1] o Significant reduction in WOMAC pain from baseline at 26 weeks.[1] o Significant reduction from baseline in WOMAC pain scores with DUROLANE versus steroid at week 26 (p=0.034).[1] **Add Note*:*** *Based on OMERACT-OARSI responder rate at 26 weeks; MPA, methylprednisolone acetate. †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]

Graphic [Leighton 2014: 6a]	 Effect-sizes for WOMAC domains with 95% Confidence Interval during the blinded phase of the study.
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. *Osteoarthritis Cartilage.* 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009

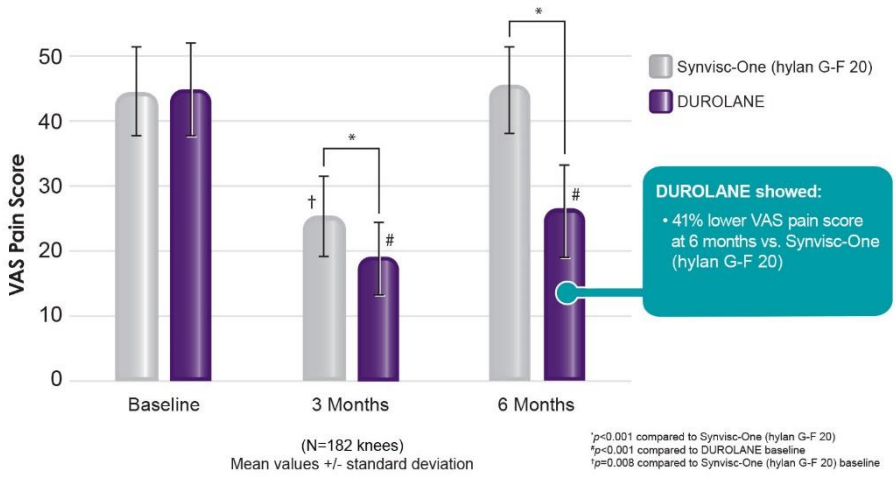
Claim	● More powerful, lasting pain relief versus MPA at 26 weeks in a prospective, randomized study.[1] ● DUROLANE is as effective as MPA at 6 weeks for WOMAC Pain responder rate.*[1] ● MPA reached maximum effect on mean WOMAC Pain scores at 6 weeks.[1] ● Results trended in favor of DUROLANE for WOMAC 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 (± 95% Confidence Interval) following double-blind treatment with eitherDUROLANE 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. *Osteoarthritis Cartilage.* 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:** *Up to 6 months based on VAS values. *Study report of more pain relief with DUROLANE for up to 6 months was based on VAS values. Comparison with hylan G-F 20 was based on a 3-injection course of Synvisc® or a one-injection course of Synvisc-One®. A three-injection course of Synvisc® is therapeutically equivalent to a one-injection course of Synvisc-One®.
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. *J Arthritis*. 2013; 2(1):1000108. doi:10.4172/2167-7921.1000108

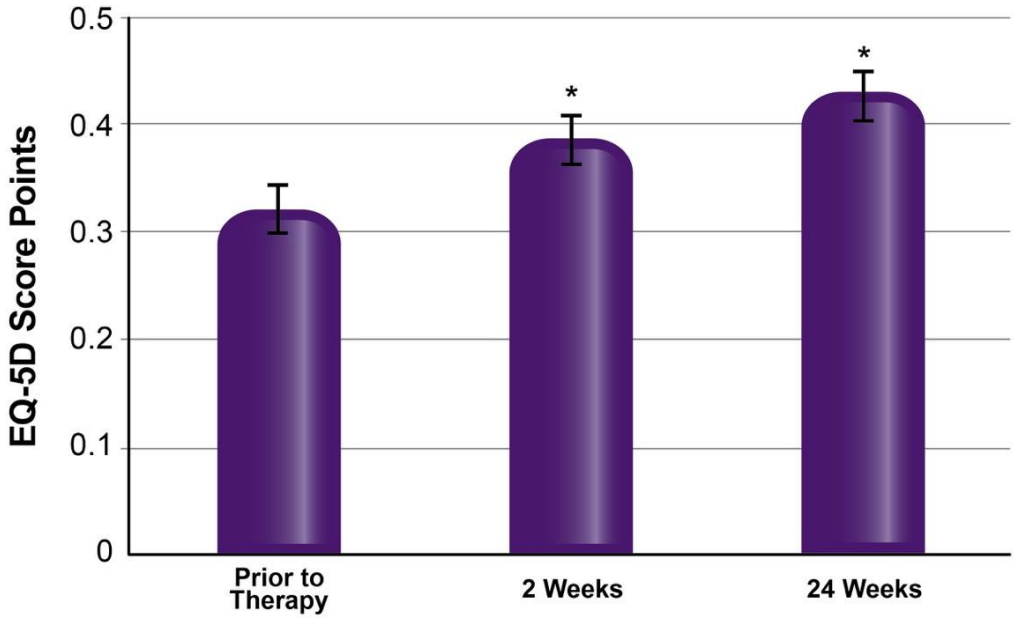
Claim	• A single-injection hyaluronic acid (HA) treatment that has proven: o Greater reduction in knee pain versus Synvisc-One® (hylan G-F 20)*[1] o Longer lasting pain relief versus steroid at 26 weeks.[2] o Clinically equivalent performance to five-injection HA therapy[3,4] **Add Note:** *Study report of more pain relief with DUROLANE for up to 6 months was based on VAS values. †Comparison with hylan G-F 20 was based on a three-injection course of Synvisc® or a one-injection course of Synvisc-One®. A three-injection course of Synvisc® is therapeutically equivalent to a one-injection course of Synvisc-One®.
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. *J Arthritis.* 2013;2(1):1000108. doi:10.4172/2167-7921.1000108 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. *Osteoarthritis Cartilage*. 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. *Arthritis Res Ther.* 2015;17(1):51. doi:10.1186/s13075-015-0557-x 4. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020.

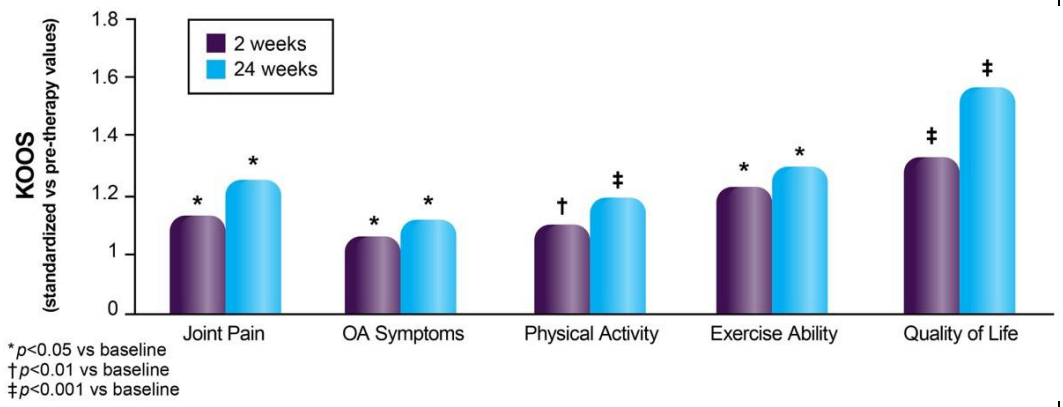
Claim	• DUROLANE offers pain relief in a prospective, randomized, head-to-head study versus Synvisc-One®.*[1] • More powerful pain relief* versus Synvisc-One®† (hylan G-F 20) in a prospective randomized study.[1] • Greater reduction in knee pain versus Synvisc-One® (hylan G-F 20)*[1] • In a study with 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 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: o 41% lower VAS pain score at 6 months versus Synvisc-One®† (hylan G-F 20)[1] **Add Note:** *Up to 6 months based on VAS values. †Study references Synvisc® & Synvisc-One®, 3 injections of Synvisc® is equivalent in volume to 1 injection of Synvisc-One®.
Graphic [McGrath 2013: 2i]	
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. *J Arthritis.* 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 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]
Graph [Krocker 2006: 2e]	 Quality of life measured using the EQ-5D questionnaire prior to therapy and at follow-up visits. Mean values ± SEM *p<0.001
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. *Z Rheumatol.* 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 and Osteoarthritis Outcome Score (KOOS) parameters from 2 weeks.[1]
Graph [Krocker 2006: 2d]	 Mean values ± SEM. 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. *Z Rheumatol.* 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 knee pain through a single intra-articular injection of synthetic hyaluronic acid. *Z Rheumatol.* 2006;65(4):327-31. doi:10.1007/s00393-006-0063-2

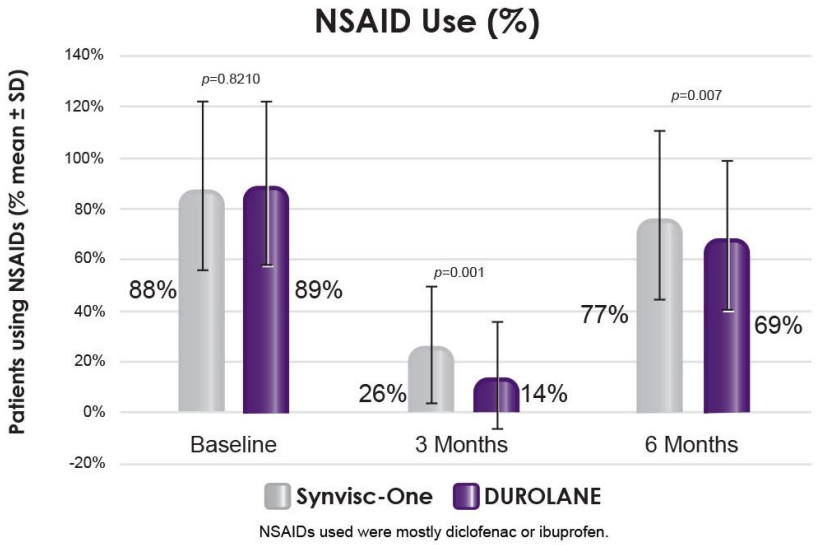
Claim	• Injections of supplemental DUROLANE may help delay the need for TKR surgery.[1] • Repeated injections of DUROLANE therapy may delay the need for TKR surgery.[1]
Reference	1. Romero Jurado M, Enrique Fidalgo A, Rodríquez Villar V, Mar Medina J, Soler López B. Factors related with the time to surgery in waiting-list patients for knee prostheses. *Reumatol Clin.* 2013;9(3):148-55. doi:10.1016/j.reuma.2012.09.003

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. *Z Rheumatol.* 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. *J Arthritis*. 2013;2(1):1000108. doi:10.4172/2167-7921.1000108

Claim	• DUROLANE provides a significant reduction in analgesia use (p=0.004).[1,2]
Graphic [Krocker 2006: 3f]	Significant Reduction in Analgesic Use[1] 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. *Z Rheumatol.* 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:** *Comparison with hylan G-F 20 was based on a three-injection course of Synvisc® or a one-injection course of Synvisc-One. A three-injection course of Synvisc is therapeutically equivalent to a one-injection course of Synvisc-One.*
Graph [McGrath 2013: 3e]	
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. *J Arthritis*. 2013;2(1):1000108. doi:10.4172/2167-7921.1000108

Claim	• One injection of DUROLANE provided up to 6 months of pain relief, reducing the need for rescue medications.[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. *Arthritis Res Ther.* 2015;17(1):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 osteoarthritis.[1-6]
Reference	**Knee:** 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. *Open Access Rheumatol.* 2018;10:43-54. doi:10.2147/OARRR.S162127 **Hip:** 2. Conrozier T, Couris CM, Mathieu P, et al. Safety, efficacy and predictive factors ofefficacy of a single intra-articular injection of non-animal-stabilized-hyaluronic-acidin the hip joint: results of a standardized follow-up of patients treated for hip osteoarthritis in daily practice. *Arch Orthop Trauma Surg*. 2009;129(6):843-8. doi:10.1007/s00402-008-0778-4 3. Berg P, Olsson U. Intra-articular injection of non-animal stabilised hyaluronic acid(NASHA) for osteoarthritis of the hip: a pilot study. *Clin Exp Rheumatol.* 2004;22(3):300–6. **Thumb:** 4. Velasco E, Ribera MV, Pi J. Single-arm open-label study of Durolane (NASHA nonanimal hyaluronic acid) for the treatment of osteoarthritis of the thumb. *Open Access Rheumatol*. 2017;9:61-6. doi:10.2147/OARRR.S128675 **Shoulder:** 5. McKee MD, Litchfield R, Hall JA, Wester T, Jones J, Harrison AJ. NASHA hyaluronic acid for the treatment of shoulder osteoarthritis: a prospective, single-arm clinical trial. *Med Devices (Auckl).* 2019;12:227-34. doi:10.2147/MDER.S189522 **Ankle:** 6. Younger ASE, Penner M, Wing K, et al. Nonanimal hyaluronic acid for the treatment of ankle osteoarthritis: a prospective, single-arm cohort study. *J Foot Ankle Surg.* 2019;58(3):514-8. doi:10.1053/j.jfas.2018.10.003

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; 2020. 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. *Osteoarthritis Cartilage*. 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. *Arthritis Res Ther.* 2015;17(1):51. doi:10.1186/s13075-015-0557-x 2. DUROLANE [package insert]. Durham, NC: Bioventus LLC; 2020.

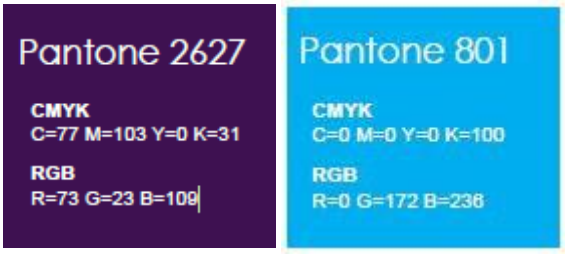
Claim	DUROLANE Safety ● Available worldwide since 2001, with a low incidence of post-market adverse event reports.[1] ● A history of safe use[1,2] ● DUROLANE has been evaluated in ten Level 1 clinical studies on OA knee pain. All treatment-related adverse events were local and transient, and most were 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. *Osteoarthritis Cartilage.* 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. *Stem Cells Transl Med.* 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(1):51. doi:10.1186/s13075-015-0557-x 7. Vega A, Martin-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):157-64. doi:10.1186/2047-783x-14-4-157 12. Altman RD, 11. Åkermark C, Beaulieu AD, Schnitzer T, Durolane International Study Group. 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

Claim	• A single injection of HA (NASHA®) in the setting of hip joint OA was both safe and efficacious.[1]
Reference	1. Long DM, Fitzpatrick J. Safety and efficacy of a single intra-articular injection of hyaluronic acid in osteoarthritis of the hip: a case series of 87 patients. *BMC Musculoskelet Disord.* 2021;22(1):797. doi:10.1186/s12891-021-04672-0

10. DUROLANE WRITING GUIDELINES

1	Name Usage 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 lower case 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	Trademark Usage 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	Bioventus Trademark Usage Bioventus and the Bioventus logo design have be submitted for trademarking in multiple geographies. Currently, the mark is a registered trademark in the European countries listed below. Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, The Netherlands, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Sweden, Switzerland,Turkey, and United Kingdom For all European materials, the Bioventus logo is a registered trademark and should include the ®. For all other territories, the Bioventus logo is a trademark and should include the ™. If something will be available for European AND other territories, use the ™ designation.

	Notification of the mark should be written on the document (space permitting) and should read assuch: <u>For European materials, use either:</u> • The Bioventus logo is a registered trademark of Bioventus LLC. • Bioventus is a trademark and the Bioventus logo is a registered trademark of BioventusLLC. • Bioventus, the Bioventus and the DUROLANE logo are registered trademarks of Bioventus LLC.
4	<u>DUROLANE URL</u> www.DUROLANE.com
5	<u>DUROLANE Color Palette</u> Consistent use of color across all media is essential to the integrity of the DUROLANE brand. Thecolors below are the approved primary and secondary color variations for print (CMYK) and web (RGB) formats. Note that no other color specifications should be utilized. Do not change color tints or shades ofthe logo elements, regardless if they are within the color palette or not. These can be used in overall design and in charts and graphs. Primary  Secondary 

6	Address Format **Bioventus Coöperatief U.A.** Taurusavenue 31 2132 LS Hoofddorp The Netherlands **Customer Care** **T:** 00800 02 04 06 08 (ttf) **E:** customercare-international@bioventusglobal.com
7	Telephone Format Europe **Customer Care** **T:** 00800 02 04 06 08 (ttf) **E:** customercare-international@bioventusglobal.com
8	Writing Style • Orthopaedic (with the "a") is the appropriate spelling of the name in Bioventus materials • As a company, Bioventus uses the US spelling conventions for all other words • BioSphere, the emblem within the Bioventus logo, includes a capital "S" in its name. • Century Gothic – Headlines/Section Headers/Callouts Century Gothic should be used for all headlines and section headers and can be used for callouts. When used as a headline it should be Pantone 2627 or reversed out of a bar of one of the primary colors. It should always be typeset in Century Gothic Regular. Bold, italic and bold italic are permitted to add emphasis only. For instance, a callout would be typeset in Century Gothic Italic. Arial - Subheads/Body/Lists/Callouts Arial should be used for all subheads, tables, body copy and can be used for callouts as well. When used as a subhead it should be either Pantone 1675, Black or Cool Grey 9. It should always be differentiated from the headline by size and color. Note: For black and white pieces **ONLY** — headlines should be 100 percent black, subheads and body copy should be 75% black, as it is in this copy.

9	Fonts for Marketing Materials Century Gothic font should be used for all headlines, while Arial would serve as body copy. If a subhead, multiple headers, raised quotes, etc. are used in the printed pieces, these can either be Century Gothic or Arial based on the design of the piece. If any text in the document is printed in bold, then the Century Gothic headline of the document must also be in bold.

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) CITATATION STYLE

- Each reference is numbered, and the superscript number in the text is used to indicate thereference
- Superscript numbers are placed outside periods and commas, and inside 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 thereference 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. *Med Educ.* 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. *J Am Coll Surg*. 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 in9-13-year-olds. *J Hum Nutr Diet*. 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. *JEMS* [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 alater page write the page numbers likeD1, D5	Wolf W. State's mail-order drug plan launched. *MinneapolisStar Tribune*. May 14, 2004:1B.

Citation Type	Example
Newspaper article – online	Pollack A. FDA approves new cystic fibrosis drug.*New York Times*. January 31, 2012. Accessed February 1, 2012. www.nytimes.com/2012/02/01/business/fda-approves-cystic-fibrosis-drug.html
Websites	Centers for Disease Control and Prevention. Outbreak notice: Cholera in Haiti. Last updated January 9, 2012. Accessed February 1, 2012. wwnc.cdc.gov/travel/notices/outbreak-notice/haiti-cholera.htm

Entire book – in print	Modlin J, Jenkins P. *Decision Analysis in Planningfor a Polio Outbreak in the United States*. San Francisco, CA: Pediatric Academic Societies; 2004.
Book chapter – in print	Solensky R. Drug allergy: desensitization and treatmentof reactions to antibiotics and aspirin. In: Lockey P, ed. *Allergens and Allergen Immunotherapy*. 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 for Automotive Medicine; September 2002; Tempe, AZ.

Document Detail

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Owner: NICOLE.SGHERZA Nicole Sgherza

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Reference

Document No.	Content Type	Relation	Fixed Rev	Status
SMK-000986 [C]	DOCUMENT	Sub Document	No	RELEASED
Title:DUROLANE Website - UK				
WIN-000266 [B]	DOCUMENT	Related	No	RELEASED
Title:How to set up and review Promotional Materials in PleaseReview				
SMK-002448 [A]	DOCUMENT	Related	No	RELEASED
Title:DUROLANE OA Knee Poster AAP Indirect Knee Master				
SMK-002451 [A]	DOCUMENT	Related	No	RELEASED
Title:DUROLANE OA Knee Poster AAP Indirect Hip and Knee Master				
SMK-002428 [A]	DOCUMENT	Related	No	RELEASED
Title:DUROLANE OA Poster AUS				
SMK-002452 [A]	DOCUMENT	Related	No	RELEASED
Title:DUROLANE OA Knee Poster Taiwan				
Q105007-BC [E]	DOCUMENT	Related	No	RELEASED
Title:Legal, Medical, and Regulatory (LMR) Approval Process				
0059335 [A]	DOCUMENT	Related	No	RELEASED
Title:Dissemination of Promotional Material				

Revision Notes

Document Build No.	Access Activity	Accessed By	Accessed Date
1	Check In	NICOLE.SGHERZA	09-Jan-2023
Note:			
2	Check In	NICOLE.SGHERZA	10-Jan-2023
Note:			
3	Check In	NICOLE.SGHERZA	12-Jan-2023
Note:			

Review

Build No.: 3 **Closed Date:** 1/18/2023 6:26:54PM

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	12-Jan-2023 11:15 pm	AMBER.PLOTNER
Note To Reviewer: all PR comments addressed in CO				
Note From Reviewer:Approved as CA				
1	BV Doc Owner / Author BV Doc Owner / Author	NICOLE.SGHERZA Nicole Sgherza	13-Jan-2023 5:05 pm	NICOLE.SGHERZA
Note To Reviewer: new doc owner - transferred from Monica Rai				
Note From Reviewer:approved				
1	BV Medical Affairs BV Medical Affairs	HELEN.SMITH Helen Smith	13-Jan-2023 10:56 am	HELEN.SMITH
Note To Reviewer:				
Note From Reviewer:approved by medical affairs (helen smith)				
1	BV Regulatory Affairs BV Regulatory Affairs	LIZZIE.FIELDS Lizzie Fields	18-Jan-2023 2:34 pm	LIZZIE.FIELDS
Note To Reviewer:				
Note From Reviewer:Approved by RA				
1	BV Legal BV Legal	TOM.BRADY Thomas C Brady	17-Jan-2023 8:45 pm	TOM.BRADY
Note To Reviewer:				
Note From Reviewer:approved, legal, tom brady				
2	BV Configuration Analyst BV Configuration Analyst	AMBER.PLOTNER Amber Plotner	18-Jan-2023 6:26 pm	AMBER.PLOTNER
Note To Reviewer:				
Note From Reviewer:Approved as CA				