Clinical Evaluation Report

DUROLANE

Prepared for:

Bioventus LLC
4721 Emperor Boulevard
Suite 100
Durham, NC 27703
USA

Prepared by:

Jon E. Block, Ph.D.
2210 Jackson Street
Suite 401
San Francisco, CA 94115
USA
415-775-7947
415-928-0765 facsimile
jb@drjonblock.com

1 SUMMARY

1.1 Overview

The primary objective of this clinical evaluation report (CER) is to evaluate, interpret and summarize the peer-reviewed literature related to DUROLANE® and DUROLANE® SJ (hereafter referred to as DUROLANE or DUROLANE product family, where appropriate) published in English-language medical journals from April 1, 2014 to March 31, 2017. This CER was developed in compliance with MEDDEV 2.7/1 revision 4 guidelines and is an update of the clinical experience associated with the product since the last clinical evaluation was performed as part of the DUROLANE product family Design Dossier Supplement 4 – EC 587693.

DUROLANE is a well established device in commercial use since 2001. It is a member of the family of hyaluronic acid (HA) products that provide viscosupplementation to arthritic joints to mitigate pain and improve function. HA constitutes a natural part of the synovial fluid and acts in the joints both as a lubricant of cartilage and ligaments and as a shock absorber. Injections of HA in the joint to restore the viscosity and elasticity can diminish the pain and improve the mobility of the joint.

HA is identical in all living organisms. It is a natural polysaccharide that is present throughout the tissues of the body, with particularly high concentrations in the synovial fluid and the skin. DUROLANE is composed of biosynthetically produced HA which has been purified and stabilized. DUROLANE is degraded in the body by the same metabolic pathway as endogenous hyaluronic acid.

1.2 Summary of Clinical Findings

A systematic literature search was undertaken to fulfill the pre-specified scope of this CER. Ninety clinical articles on HA viscosupplementation were eligible for inclusion in this CER based on pre-specified search criteria.

Clinical evaluation of all articles concluded that DUROLANE is a well-established device and the compilation of studies included in the CER continue to support the current indications for use. Notably, recently published cohort studies utilizing large administrative databases have validated the safety and effectiveness of HA viscosupplementation for joint arthritis in real-world scenarios, including a significant delay in the need for total joint replacement procedures. This is important pragmatic evidence to support the continued use of HA viscosupplementation for its intended use. The safety profile for HA is good with only minor and rare device-related adverse events, complications or other safety considerations.

2 SCOPE OF THE CLINICAL EVLUATION

The scope of this CER can be found in Appendix 1 and, along with additional collateral (Appendix 1), was provided to the evaluator prior to the initiation and execution of this clinical evaluation. Sections 2.1 through 2.6 below summarize the primary components of the project scope.

2.1 Name of the Device

DUROLANE

2.2 Manufacturer

Bioventus LLC
4721 Emperor Boulevard
Suite 100
Durham, NC 27703
USA

2.3 Device description

DUROLANE contains 20 mg/ml of stabilized non-animal hyaluronic acid in buffered physiological sodium chloride solution pH 7. DUROLANE is a sterile, transparent viscoelastic gel supplied in either a 3 ml or 1 ml (DUROLANE SJ) glass syringe. The product is for single use only.

The DUROLANE 3ml product configuration is intended to be used for intra-articular injection for the symptomatic treatment of mild to moderate knee or hip osteoarthritis. Additionally, DUROLANE is intended to be used for intra-articular injection for symptomatic treatment of mild to moderate osteoarthritis of indicated synovial joints, and for pain following arthroscopic procedures.

The 1 ml product configuration, DUROLANE SJ (small joints) is intended to be used for the same indications, but in smaller indicated synovial joints.

Both products are to be injected by an authorized physician, or in accordance with local legislation.

2.4 Device claims, indications, safety precautions/contraindications

DUROLANE 3 ml is indicated for the 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 three months of the procedure.

DUROLANE SJ (1 ml) is indicated for the same indications, but is limited to the smaller synovial joints, excluding the knee, hip, and shoulder synovial joints.

2.4.1 Contraindications

There are no known contraindications to the use of DUROLANE.

2.4.2 Warnings

- 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.

- Do not re-sterilize DUROLANE as this may damage the product.

2.4.3 Precautions

- DUROLANE should be used with caution in patients with venous or lymphatic stasis present in the leg.

- DUROLANE has not been tested in pregnant or lactating women or in children.

- A separate syringe of DUROLANE must be used for each individual joint to be treated.

- As with any invasive joint procedure there is a small risk of infection.

- DUROLANE should not be injected if the patient is known to be sensitive to hyaluronic acid based products.

- Local anesthetics should not be used if the patient is known to be allergic or sensitive to local anesthetics.

- Injection under fluoroscopic control and with the use of a contrast medium should not be made if the patient is known to be allergic or sensitive to the contrast medium.

- In clinical studies, reinjections in the knee have not been studied with a shorter interval between first and second injection than 6 months.

- Increase in injection pressure may indicate incorrect extra-articular placement of the needle or over filling of the joint.

- The effectiveness of DUROLANE following arthroscopic procedures for diagnosis or examination purposes only or in absence of concomitant osteoarthritis of the joint has not been established.

- DUROLANE should be used with caution in patients with pre-existing chondrocalcinosis as injection may lead to an acute attack of the condition.

2.5 Instructions for use

DUROLANE is a single injection, single dose preparation and should only be injected once per treatment course. The recommended dose is 3 ml per knee, hip or shoulder joint. The recommended dose is 1-2 ml for intermediate joints (e.g., elbow, ankle) and approximately 1 ml for small synovial joints (e.g. thumb).

DUROLANE is supplied in a 3 ml glass syringe (1 ml for DUROLANE SJ) with a Luer-lok fitting, packed in a blister pack. The contents of the syringe are sterile. The exterior of the syringe is not sterile.

DUROLANE is intended for single use and should not be re-sterilized. It should be used immediately after the syringe has been removed from its packaging. If the blister package or syringe is opened or damaged, do not use.

The syringe and any unused material must be discarded immediately after the treatment session and must not be reused due to risk of contamination of the unused material and the associated risks including infections. Disposal should be in accordance with accepted medical practice and applicable national, local or institutional guidelines.

DUROLANE should be stored, in its original packaging, up to 30 degrees C. The expiry date is indicated on the package and should not be used beyond that date. Protect from freezing.

2.5.1 General administration information

- DUROLANE should only be injected by an authorized physician (or in accordance with local legislation), familiar with intra-articular injection technique for the synovial joint intended to be treated, and in facilities well suited for intra-articular injections.
- DUROLANE should be injected using strict aseptic technique.
- DUROLANE should be injected into the joint cavity only.
- Intra-articular injection in certain synovial joints will require image guidance to ensure accurate placement and avoidance of damage to adjacent vital structures.
- The route for intra-articular injection with or without image guidance should be chosen so that damage to adjacent vital structures is avoided.
- The injection site should be swabbed with alcohol or other suitable antiseptic solution before injection.
- Remove joint effusion, if present, before injecting DUROLANE. The same needle should be used for both removal of effusion and injection of DUROLANE.
- The recommended needle size is 18 to 22 G and with adequate length.
- Use of smaller needles increases pressure required to deliver the product.

2.5.2 Additional information for treatment of synovial joints requiring image guidance

- The intra-articular injection in the hip joints should be given under fluoroscopic control (preferably with a contrast medium) or ultrasonographic control in order to assure correct location of the needle in the joint cavity.

- Guidance of other synovial joints is at the discretion of the treating physician.

- Injection discomfort can be minimized by use of topical freezing agents or subcutaneously delivered local anesthetics.

- Image guided injection should only be performed by physicians experienced in this type of administrations.

2.5.3 Additional information for treatment post arthroscopy

- Following the arthroscopic procedure, intra-articular injection should be performed outside the sterile field as the exterior of the syringe is not sterile.

- Joints that typically undergo arthroscopic procedures are the knee, hip, shoulder, elbow, ankle, and wrist joints.

2.5.4 Patient instructions

- As with any invasive joint procedure it is recommended to avoid strenuous activity (e.g. tennis, jogging or long walks) the first two days after the injection.

- Some transient reactions related to the injection of DUROLANE, such as pain and/or swelling/stiffness of mild to moderate intensity during the first week following the injection can be anticipated. If the symptoms last for more than a week a physician should be contacted.

2.6 Regulatory history

The DUROLANE product family are CE-marked medical devices fulfilling the requirements of MDD 93/42/EEC. DUROLANE 3 ml was originally CE marked on May 8, 2001. The product was transferred to Smith & Nephew (from Q-Med, the original developer/manufacturer of the product) on May 1, 2007.

Expanded indications into its current list of indicated synovial joints and for post-arthroscopic use was granted September 22, 2010. DUROLANE SJ was added to the product portfolio on February 11, 2011. The CE mark was transferred to its current owner, Bioventus LLC, on November 7, 2012.

The most recent design dossier supplement (and last update to the clinical information supporting the product) was associated with Supplement #4 (related to a change in the raw hyaluronic acid supplier); the supplement was approved on July 29, 2016.

3 CLINICAL BACKGROUND, CURRENT KNOWLEDGE, STATE OF THE ART

3.1 Description of medical condition

Osteoarthritis is the leading cause of disability in adults and is characterized by progressive joint pain and dysfunction due to subchondral bone damage, articular cartilage loss, inflammation/synovitis, and osteophyte formation. HA is a component of synovial fluid that acts as a joint lubricant during shear stress and a shock absorber during compressive stress. Patients with OA exhibit reductions in the concentration and molecular weight of endogenous HA. Intra-articular injection of exogenous HA replaces this deficit and stimulates production of endogenous HA, which may alleviate symptoms of knee OA via inhibition of chondrodegradative enzymes and inflammatory processes, stimulation of chondrocyte metabolism, and synthesis of articular cartilage matrix components.[1]

3.2 Description of therapeutic options

In addition to HA injections, the Osteoarthritis Research Society International (OARSI) has developed expert consensus guidelines for the non-surgical management of knee OA.[2] Appropriate non-surgical treatment modalities and therapeutic options for all individuals with knee OA include biomechanical interventions, intra-articular corticosteroids, exercise (land-based and water-based), self-management and education, strength training, and weight management. Treatments appropriate for specific clinical sub-phenotypes include acetaminophen (paracetamol), balneotherapy, capsaicin, cane (walking stick), duloxetine, oral non-steroidal anti-inflammatory drugs (NSAIDs; COX-2 selective and non-selective), and topical NSAIDs. Treatments of uncertain appropriateness for specific clinical sub-phenotypes include acupuncture, avocado soybean unsaponfiables, chondroitin, crutches, diacerein, glucosamine, opioids (oral and transdermal), rosehip, transcutaneous electrical nerve stimulation, and ultrasound. Treatments judged not appropriate included risedronate and electrotherapy (neuromuscular electrical stimulation).

3.3 Safety and adverse events

The majority of the reported adverse reactions in clinical studies of DUROLANE used in the knee and hip joints have been described as transient pain, swelling and/or stiffness localized to the joint. These adverse reactions were of mild or moderate intensity and only occasionally required treatment with painkillers or NSAIDs.

The use of other HA preparations used in support of the products' expanded indications into other joints and for post-arthroscopic use did not reveal any additional unique adverse events.

None of the other adverse reactions that have been reported were interpreted as acute inflammatory arthritis or allergic reactions and they did not need medical attention in the form or surgical intervention, systemic or intra-articular steroids or antibiotics.

The safety and effectiveness of DUROLANE concomitantly with other intra-articular injectables have not been established.

3.3.1 Adverse events

Two systematic reviews included in this CER specifically addressed adverse event risk associated with HA injections.[3, 4] Using meta-analytical techniques to assess the safety and effectiveness of US-approved HA products, Strand et al[3] evaluated 29 studies involving 2,673 HA treated patients. There were no statistically significant differences between HA viscosupplementation and saline control injections for any safety outcome, with absolute risk differences of 0.7% (95% CI: -0.2 to 1.5%) for serious adverse events, 0% (95% CI: -0.4 to 0.4%) for treatment-related serious adverse events, 0% (95% CI: -1.6 to 1.6%) for patient withdrawal, and 0.2% (95% CI: -0.4 to 0.8%) for adverse event-related patient withdrawal.

Similarly, Bannuru et al[4] evaluated 74 studies involving 13,032 HA treated patients and found that overall incidence of local reactions reported across all products was 8.5%. Commonly reported adverse events were transient local reactions, such as pain, swelling and arthralgia, which subsided rapidly. None of the HA products were statistically significantly different from saline injections or from each other with regard to incidence of adverse events. Three treatment-related serious adverse events were reported among 9,214 patients (0.03%).

3.3.2 Complications

Complications related to HA administration are rare. The current CER identified only a single case report of late hemorrhagic pseudo-septic arthritis encountered during TKA due to HA viscosupplementation using the multi-injection Orthovisc product.[5] The authors findings included: (1) acute and chronic inflammatory cells on frozen section, (2) synovitis with hemosiderin deposition, and (3) blackened cartilage with iron deposition on permanent histopathology.

3.3.3 Types of users

DUROLANE should only be injected by an authorized physician (or in accordance with local legislation), familiar with intra-articular injection technique for the synovial joint intended to be treated, and in facilities well suited for intra-articular injections.

4 DEVICE UNDER EVALUATION

4.1 Type of evaluation

This CER is based on peer-reviewed clinical literature published in English-language medical journals between April 1, 2014 (date following submittal of the last Design Dossier supplement) and March 31, 2017. This CER represents an update for a well-established medical device.

4.2 Essential requirements supported by this CER

This CER supports the following Essential Requirements of the MDD for the DUROLANE device: MDD Annex 1, Sections 1, 3, 4 and 6.

4.3 Clinical data generated and held by the manufacturer

The manufacturer disclosed reference to three post-market clinical follow-up studies. Two of these studies are complete and one is ongoing. Both completed studies employed the DUROLANE SJ product. The first completed study was entitled *Study of the Clinical and Biomechanical Effectiveness of DUROLANE SJ in Rhizarthrosis: Prospective, open, non-comparative study* (DURE04), with study dates, 21 May 2013 (first patient, first visit) to 18 July 2014 (last patient, last visit).

This was a prospective, open-label, non-comparative study conducted in Spain in 36 subjects with rhizarthrosis comparing signs and symptoms before and after a single injection of DUROLANE SJ in the affected hand. Subjects were assessed pre-treatment and at 1, 3, and 6-months post-treatment. Each subject received one injection of DUROLANE SJ in the TMC joint. Outcomes included VAS pain, QuickDASH questionnaire, Kapandji thumb opposition test, radial abduction and MCP flexion, and grip and pinch strength. The results were published by Velasco et al.[6] In brief, pain in the injected hand improved significantly both clinically and statistically with an overall reduction in VAS pain of 2.00 units over the 6 month study period, equating to a 27.8% change from baseline value ($p<0.0001$). The number of VAS pain responders increased over the course of the study, with varying magnitudes of pain reduction. Only 2 subjects were noted as not having any level of pain response.

Functioning based on the QuickDASH questionnaire and Kapandji thumb opposition test demonstrated statistically significant improvements over 26 weeks. Biomechanical functioning based on radial abduction, MCP flexion, and clamp (pinch) strength were also statistically significantly improved over 26 weeks. Fist (grip) strength was the only functional measurement not statistically significant.

A total of five AEs were reported in four patients (11.4%). All five AEs occurred on day 1. None were classified as serious or interpreted as allergic reactions. Two of the AEs occurred in one patient: pain and swelling. Both of these AEs were of moderate intensity and both were related to study treatment. Three out of the four patients with AEs were treated with analgesic medication or nonsteroidal anti-inflammatory drugs, and all of the AEs except one resolved within a week. The exception was pain in one patient that lasted for 95 days.

The second completed study was entitled *A 26 Week Single-Center Prospective Open-Label Clinical Study Evaluating a Single IA Injection of DUROLANE SJ 1 mL for Treatment of Osteoarthritis Pain of the Ankle* (13DUR502), with study dates, 24 September 2014 (first patient, first visit) to 25 August 2016 (last patient, last visit).

This was a prospective, open-label, single-cohort study to evaluate pain and disability outcomes and safety following IA injection of DUROLANE SJ 1 mL in subjects with symptomatic ankle OA followed over a 26-week period. The study consisted of a Screening/washout period, a Baseline Visit (Week 0) during which an IA ankle injection was given (the Screening and Baseline Visits may have been combined), and follow-up clinic visits at Week 6, Week 12, and Week 26 after the Baseline Visit. A total of 37 subjects were enrolled into the study at a single study center in Canada. Outcomes included the Ankle Osteoarthritis Scale (AOS) for pain and disability.

For the AOS VAS pain score, the least square mean change from baseline (CFB) over the entire 26-week period of the study was -20.5 mm with a 95% CI of -25.5, -15.6 mm (negative scores represent a decrease in pain and thus an improvement of symptoms). This represented a mean percentage change of -40.0% (95% CI: -49.9, -30.2). This magnitude of change exceeded the minimally clinically important threshold for study success of 25%. As with the AOS pain score, improvements in the AOS disability subscale score were seen across the entire 26-week study period and at each visit. The mean CFB over 26 weeks was -19.2 mm (95% CI: -24.8, -13.6), which corresponded to a percentage CFB of -34%.

Five subjects experienced a total of 7 AEs that were considered by the Investigator to be related to study drug. These events were primarily related to the injection site (3 AEs each of injection site pain and injection site joint pain; 1 AE of plantar fasciitis).

In conclusion, there was a notable improvement in subjects' ankle pain following treatment with DUROLANE SJ. In addition, improvement was observed at all time points during the study.

The single ongoing study, a *26 Week Prospective Open Label Clinical Study Evaluating a Single Intra-Articular Injection of DUROLANE 3mL for Treatment of Osteoarthritis Pain of the Shoulder* (13 DUR503) has enrolled 41 subjects at two sites in Canada with the last patient follow-up visit anticipated in July 2017. Enrollment is complete. The primary objective of this study is to evaluate the efficacy of a single intra-articular injection of DUROLANE 3mL given for the relief of pain in the treatment of symptomatic osteoarthritis of the shoulder followed over a 26-week time period. The primary outcome measure is pain on movement VAS.

The secondary objectives are to evaluate the efficacy of a single injection of DUROLANE 3mL given for treatment of symptomatic OA of the shoulder followed over a 26-week time period for

- shoulder pain at night
- shoulder range of motion
- shoulder pain rescue medication use, and,
- Safety objective include evaluation of the safety and tolerability of DUROLANE 3 mL over the 26-week time period in the shoulder joint.

4.4 Clinical data from literature

4.4.1 Search methods

A systematic literature search was conducted using MEDLINE/PUBMed and the Cochrane Library including the Cochrane Bone, Joint and Muscle Trauma Group Specialized Register (2 June 2014) and the Cochrane Central Register of Controlled Trials (The Cochrane Library 2014, Issue 5) for the period, April 1, 2014 to March 31, 2017 inclusive. The US National Library of Medicine Medical Subject Headings (MeSH) vocabulary thesaurus was used in various combinations and supplemented with free text to increase sensitivity. Searches were restricted to English-language journals only. The search strategy for each database can be found in Appendix

2. Additionally, the author manually reviewed the reference sections and citation tracking results of all included studies for articles not found during the systematic electronic search.

4.4.2 Selection of published literature

The author performed the initial screening for relevant articles based on titles and abstracts. The titles and abstracts of all the retrieved studies were screened to determine potential eligibility. The full text of each study in this shortlist was then read to determine which studies were eligible for inclusion in this CER.

Only articles published in peer-reviewed journals describing clinical findings using HA viscosupplementation for joint OA clinical management applications were included. Articles were included for devices from all manufacturers as well as articles where the commercial entity was not specified. Nonclinical, animal, and basic science articles were excluded. Book chapters, abstracts, monographs and white papers were also excluded.

4.4.3 Data extraction and management

Using a standardized data summary form, study methodology and data were extracted from each eligible article including study design, country of origin, level of evidence, sample size, device employed, summary of background characteristics, and summary of main findings.

4.4.4 Data synthesis

The level of evidence for each study was ranked using the Oxford Centre for Evidence-based Medicine (CEBM), Levels of Evidence (March 2009) provided in Appendix 3. Each article was summarized qualitatively in a study synopsis.

4.5 Summary and appraisal of clinical data

4.5.1 Search results

The systematic literature identified 90 articles of HA viscosupplementation that were eligible for inclusion in this CER based on the pre-specified search criteria. Twenty-eight articles were excluded for the following reasons: narrative review (8),[1, 7-13] unrelated topic (9),[14-22] HA utilization statistics/costs (7),[23-29] correspondence to the editor (2),[30, 31] editorial (1),[32] trial protocol (1).[33]

Of the 90 included articles, 74 involved the knee joint,[2-5, 34-103] 6 hip,[104-109] 4 ankle,[110-113] 3 temporomandibular,[114-116] 2 thumb,[6, 117] and 1 shoulder.[118]

One study evaluated use of HA for post-arthroscopic use[64]; all other articles pertained to use for osteoarthritic pain management.

4.5.2 Design of included studies

There were 22 systematic literature reviews,[2-4, 34, 40, 44, 46, 49, 52, 56, 59, 63, 66, 84, 86, 91, 93, 95, 100, 101, 105, 110] 36 randomized controlled trials, [35, 36, 47, 48, 53, 55, 57, 58, 61, 64, 65, 68, 70, 73-75, 77-80, 82, 85, 88, 90, 96-99, 102, 103, 106, 107, 113, 115-117] 5 retrospective cohort studies, [43, 54, 62, 71, 81] 15 prospective single-arm trials,[6, 38, 42, 45, 60, 67, 69, 83, 89, 104, 108, 111, 112, 114, 118] 2 prospective double-arm trials,[37, 76] 9 retrospective case series,[39, 41, 50, 51, 72, 87, 92, 94, 109] and one case report.[5]

Based on CEBM criteria, there were 22 systematic reviews of randomized controlled trials (Level Ia),[2-4, 34, 40, 44, 46, 49, 52, 56, 59, 63, 66, 84, 86, 91, 93, 95, 100, 101, 105, 110] 36 individual randomized controlled trials (Level Ib),[35, 36, 47, 48, 53, 55, 57, 58, 61, 64, 65, 68, 70, 73-75, 77-80, 82, 85, 88, 90, 96-99, 102, 103, 106, 107, 113, 115-117] 5 individual cohort studies (Level IIb),[43, 54, 62, 71, 81] and 27 case series (Level IV).[5, 6, 37-39, 41, 42, 45, 50, 51, 60, 67, 69, 72, 76, 83, 87, 89, 92, 94, 104, 108, 109, 111, 112, 114, 118]

4.5.3 Sample sizes

Sample sizes ranged from 1 patient in a case report to 50,389 included in a retrospective cohort study.

4.5.4 Participants

The total number of patients (joints) treated with HA among the 90 included articles could not be determined with precision as many of the systematic reviews evaluated the same study data, resulting in considerable overlap in patient (joint) counts.

4.5.5 Interventions

Multiple HA products and treatment regimens were involved in the 90 included articles. Due to the large number of systematic reviews/meta-analyses (n=22) that each included a variety of HA products (specified and unspecified), the distribution across product type could not be determined with precision.

4.5.6 Individual study synopses

Individual study synopses are provided in Appendix 4.

4.6 Analysis of the clinical data

4.6.1 Requirements on safety (MDD ER1)

This evaluation concludes that there are no special design features that pose special safety concerns. The risks identified in the risk management documentation and literature have been adequately addressed. All hazards and other clinical relevant information have been identified appropriately. All training requirements and other precautions are described in the IFU. There is full consistency between current knowledge, the available clinical data, the information materials supplied by the manufacturer, and the risk management documentation for the device.

4.6.2 Requirement on acceptable benefit/risk profile (MDD ER1)

This evaluation concludes that the DUROLANE product family has an acceptable benefit/risk profile. The literature evaluated in this CER shows that adverse events are rare with HAs in general and identified only one case report of a potential device-related complication for a non-DUROLANE, multi-injection product (i.e., Orthovisc).

4.6.3 Requirement on performance (MDD ER3)

The compendium of published HA studies included in this CER supports the current indications for use for DUROLANE. There are several reports of particular note.

In a large cohort study, Altman et al[43] retrospectively evaluated records in an administrative claims database of ~79 million patients, to identify all patients with knee OA who received total knee arthroplasty (TKA) during a 6-year period. Only patients with continuous plan enrollment from diagnosis until TKA were included, so that complete medical records were available. OA diagnosis was the index event and time-to-TKA was evaluated as a function of the number of HA injections. The database included 182,022 patients with knee OA who had TKA; 50,349 (27.7%) of these patients were classified as HA users, receiving ≥1 courses of HA prior to TKA, while 131,673 patients (72.3%) were HA non-users prior to TKA, receiving no HA. Cox proportional hazards modelling showed that TKA risk decreased as a function of the number of HA injection courses, if patient age, gender, and disease comorbidity are used as background covariates. Multiple HA injections were therefore associated with delay of TKA (all, $p < 0.0001$). Half of HA non- users had a TKA by 114 days post-diagnosis of knee OA, whereas half of HA users had a TKA by 484 days post-diagnosis ($\chi2 = 19,769$; $p < 0.0001$). Patients who received no HA had a mean time-to-TKA of 0.7 years; with one course of HA, the mean time to TKA was 1.4 years ($\chi2 = 13,725$; $p < 0.0001$); patients who received ≥5 courses delayed TKA by 3.6 years ($\chi2 = 19,935$; $p < 0.0001$).

The delay in TKA associated with HA injection was confirmed in a follow-up large retrospective cohort study by Ong et al.[81] Using the 5% Part B Medicare data (2005-2012) to identify knee OA patients who underwent TKA. The time from diagnosis of OA to TKA was compared between patients with HA (n=9,586) and without HA use (n=25,560), using quantile regression with propensity score adjustment. The HA cohort was associated with a longer time to TKA of 8.7 months (95% CI: 8.3-9.1 months; $p < 0.001$) compared with the no HA cohort.

There were 22 systematic reviews with quantitative meta-analysis of HA effectiveness identified in this CER and their recommendations have been mixed and discordant.[14, 32] Xing et al[93] conducted a systematic review of overlapping meta-analyses investigating the efficacy and safety of HA for knee OA and to provide treatment recommendations through the best evidence. A systematic review was conducted based on the PRISMA guidelines. The meta-analyses and/or systematic reviews that compared HA and saline placebo for knee OA were identified. Meta-analyses quality was determined according to the Jadad algorithm. Twelve meta-analyses met the eligibility requirements. Based on the weighted highest quality reviews, this systematic review of overlapping meta-analyses demonstrated that HA is an effective intervention in treating knee OA without increased risk of adverse events.

DUROLANE was evaluated specifically in a limited number of studies included in this CER.[6, 61, 98, 115] Guarda-Nardini et al[115] compared single injection DUROLANE SJ with both single injection medium molecular weight HA and 5 injection medium molecular weight HA for TMJ syndrome. Pairwise comparisons showed no differences between the two single injection interventions for pain reduction (p = 0.93). The 5 injection protocol was significantly superior to both single injection protocols (p range: 0.003 to 0.012). Zhang et al[61] compared DUROLANE with Artz for patients with knee OA and demonstrated that single injection DUROLANE was non-inferior to 5 injections of Artz over 18 and 26 weeks for pain, physical function, global self-assessment, and knee stiffness. Estades-Rubio et al[98] compared DUROLANE with Go-ON for patients with knee OA and demonstrated that WOMAC scores were significantly better for DUROLANE versus Go-ON at week 26 and the need for analgesia was significantly reduced in the DUROLANE group. Lastly, Velasco et al[6] evaluated a single injection of DUROLANE SJ in patients with thumb OA followed for 6 months. Pain improved over 6 months by –2.00, a reduction of 27.8% ($p<0.001$) and the reduction in pain exceeded 25% as early as month 1 (26.5%).

In conclusion, studies that specifically evaluated DUROLANE showed similar improvements in joint pain and function as that reported in the overall body of HA studies evaluated in this CER.

4.6.4 Requirement on acceptability of side effects (MDD ER6)

This evaluation concludes that the known side effects associated with use of HA in general and DUROLANE specifically are mild, rare, resolve quickly and are well described in the published literature and product regulatory dossiers.

5 CONCLUSIONS

The clinical evidence provided herein on the HA product class as a whole and inclusive of studies specific to the product supports DUROLANE's continual compliance with the previously identified Essential Requirements of the MDD. The risk/benefit conclusion documented in the DUROLANE risk management file is also supported by the clinical evidence and remains unchanged since the introduction of the current formulation in 2001. Bioventus has not discovered any clinical evidence that indicates that the information provided with the DUROLANE product family or current risk reduction measures are inadequate.

The DUROLANE product family is well-established and the compilation of studies included in this CER continue to support the current indications for use.

6 DATE OF THE NEXT CLINICAL EVALUATION

The DUROLANE CER shall be updated 5 years from the latter date of the inclusion period of this CER. Five years is an appropriate interval as the DUROLANE product family is well-established with an excellent safety profile.

7 DATES AND SIGNATURES

Clinical Evaluation Report completion date:

I, Jon E. Block, Ph.D., confirm and agree with the contents of and conclusions reached in this CER.

Jon E. Block, Ph.D.

Required Bioventus Signatories:

Mason W. Robbins
Regulatory Affairs Project Manager II

R. Grant Steen
Manager, Medical Affairs

Kevin Tanis
Director, Product Development and Engineering

Kim P. Kelly
Director, Regulatory and Clinical Affairs

Peter Heeckt, M.D., Ph.D.
Chief Medical Officer

8 QUALIFICATIONS OF THE EVALUATOR

Dr. Block is a leading authority on the design, conduct, interpretation and presentation of clinical trials for medical devices. He has made significant contributions to the fields of musculoskeletal medicine and emerging orthopedic medical technology with over 125 peer-reviewed publications (Curriculum Vitae, Appendix 5). He was involved in the seminal research at the University of California, San Francisco (UCSF) that validated the clinical performance of bone densitometry as the standard of care in the assessment of osteoporosis.

9 REFERENCES

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