# CLINICAL EVALUATION REPORT

## Fermathron® Product Family:

## Fermathron®

## Fermathron® Plus

**Date of issue: 18/SEP/2018**

**Version: 001**

# REVISION HISTORY

**Table 1: History table - Fermathron**

| Revision Number | Changed Section(s) | Change Description & Rationale Fermathron | Date of Change | Author of Change |
|---|---|---|---|---|
| Version 001 | n/a | Not applicable – new document | July 2013 | Dr Marie Thomas |
| Version 002 | n/a | CER update – review of clinical evidence since Version 001 of CER | November 2016 | Cheryl Lockett |

**Table 2: History table - Fermathron plus**

| Revision Number | Changed Section(s) | Change Description & Rationale Fermathron plus | Date of Change | Author of Change |
|---|---|---|---|---|
| Version 001 | n/a | Not applicable – new document | July 2013 | Dr Marie Thomas |
| Version 002 | n/a | Further analysis and assessment of literature concerning synovial joints other than the knee, results of Dr. Kooijman clinical risk assessment | August 2012 | Dr Marie Thomas |
| Version 003 | n/a | Minor changes and corrections that do not affect the clinical content of the evaluation significantly and therefore do not require approval by a clinician | November 2012 | Dr Marie Thomas |
| Version 004 | n/a | Minor changes and corrections that do not affect the clinical content of the evaluation significantly and therefore do not require approval by a clinician | March 2013 | Dr Marie Thomas |
| Version 005 | n/a | CER update – review of clinical evidence since Version 004 of CER. As nothing has come to light during the evaluation which would in any way imply an adverse impact on the safety or performance of Fermathron plus additional review by a clinician was deemed unnecessary. | June 2013 | Cheryl Lockett |

**Table 3: History table - Combined Fermathron and Fermathron plus**

| Revision Number | Changed Section(s) | Change Description & Rationale Fermathron and Fermathron plus | Date of Change | Author of Change |
|---|---|---|---|---|
| Version 001 | All | Complete update to comply with MEDDEV 2.7.1 Rev 4 & to merge Fermathron and Fermathron plus CER's | December 2017 | Emma McColm |

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# REFERENCE LIST

### Table 4: Reference list of existing documents

| Consecutive No. | Document | Version | Creation/issue date |
|---|---|---|---|
| D01 | IFU: Fermathron | 032-45-K5 | 01/2015 |
| D02 | IFU: Fermathron Plus | 272-45-K3 | 01/2015 |
| D03 | Fermathron Family Brochure: Fermathron, Fermathron Plus and Fermathron One | 0425.1 EMEA | 05/2016 |
| D04 | Fermathron Patient Brochure | 0426.1-EMEA | 05/2016 |
| D05 | Fermathron Surgeon Brochure | 0427.1-EMEA | 04/2016 |
| D06 | Fermathron Clinical Evidence Flyer | 0428.1-EMEA | 04/2016 |
| D07 | Literature search Report | 001 | 12/2017 |
| D08 | Fermathron Risk Assessment | V004 | 11/ 2016 |
| D09 | Fermathron Risk Management Report | V005 | 11/2016 |
| D10 | Fermathron Plus Risk Assessment | V003 | 11/2013 |
| D11 | Fermathron Risk Management Report | V005 | 11/2013 |
| D12 | Post Market Surveillance minutes | N/A | 07/2018 |

# TERMS AND DEFINITIONS

**Table 5: Terms and definitions**

| Term | Definition |
|---|---|
| ACS | Autologus conditioned serum |
| AE | Adverse event |
| CAPA | Corrective and preventive action |
| CER | Clinical Evaluation Report |
| CS | Corticosteroids |
| CZM | Carl Zeiss Meditec AG |
| EEA | European economic area |
| EQ-VAS | Visual analogue scale to assess health status and well-being |
| ESCEO | European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis |
| EUROQOL | European Quality of Life Scale |
| HA | Hyaluronic Acid/Hyaluronan/ Sodium Hyaluronate |
| HMW | High Molecular Weight |
| IA | Intra-articular |
| IA-HA | Intra-articular Hyaluronic Acid viscosupplementation |
| IFU | Instructions for Use |
| IL | Interleukin |
| ISO | Internation Standards Organisation |
| ITT | “intent to treat” population |
| kDa | Kilo Dalton ($10^3$ Daltons) |
| KL | Kellgren-Lawrence |
| LMW | Low Molecular Weight |
| MW | Molecular Weight |
| MAUDE | Manufacturer And User Device Experience |
| MHRA | Medicines and Healthcare products Regulatory Agency: UK Competent Authority |
| MDD ER | Medical device directive 93/42/EEC; Essential Requirement |
| NaCl | Sodium Chloride |
| NSAID | Non-steroidal Anti-inflammatory drug |

| Term | Definition |
|---|---|
| OA | osteoarthritis |
| OARSI | Osteoarthritis Research Society International |
| OMERACT | Outcome Measures in Rheumatoid Arthritis Clinical Trials |
| PMCF | Post-market clinical follow-up |
| PMS | Post market surveillance |
| PRP | Platelet-rich Plasma |
| RCT | Randomised Controlled Trial |
| SF | Synovial Fluid |
| TENS | Transcutaneous electric nerve stimulation |
| TKR | Total knee replacement |
| VAS | Visual Analogue Scale |
| WOMAC | Western Ontario and McMaster Universities Osteoarthritis Index |

# 1. EXECUTIVE SUMMARY

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|---|---|
| **Device(s) under consideration** | **Fermathron®**<br>**Fermathron® plus** |
| **Intended use** | **Fermathron:** For the relief of pain and stiffness of the knee, hip, ankle and shoulder joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint.<br><br>**Fermathron plus:** For the relief of pain and stiffness of the knee, hip and and ankle joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint. |
| **Equivalent device(s)** | Fermathron: **Hyalart (or Hyalgan)** manufactured by Fidia Farmaceutici<br>Fermathron plus: **Orthovisc** manufactured by Anika Therapeutics Inc. |
| **Literature search and appraisal** | A literature search was performed in order to identify, appraise and analyse clinical data in accordance with MEDDEV 2.7.1 rev 4. The following literature sources were used to identify data:<br>- PubMed<br>- MAUDE adverse events database<br>-Unpublished data including evaluation of Hyaltech PMS data for Fermathron/Fermathron plus.<br>Search terms are detailed in section 5 and covered concepts that take into account the device in question and the established devices already on the market and used in clinical practice and with which equivalence can be demonstrated in terms of technology, critical performance, design, principles of operation, biological safety, population involved, conditions of use and clinical purpose.<br>After screening the results yielded 8 meta-analyses; 8 prospective, randomised, comparative studies; 1 prospective non-randomised comparative study, 4 retrospective comparative data analyses; 3 retrospective data analyses and 13 reviews and 4 other publication types.<br>Period covered by searches : May 2012 until October 2017<br>The overall normalised appraisal score for the clinical studies was 6.29 with a minimum of 2.11 and a maximum of 10. |
| **Safety and performance clinical data** | A randomised, controlled, observer-blind clinical investigation comparing Fermathron with Hyalart (Hyalgan) was undertaken (CT9705, McDonald et. al. 2000). Five intra-articular injections were administered and followed up until 3 months post-injection. A reduction in the Lequesne Index and visual analogue scale for knee pain was observed in both products, which were similar in performance. Both products were well tolerated and showed clinically significant benefits for up to 6 months after treatment. |

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| | In a randomised, controlled, double-blind trial, 196 patients with symptomatic knee osteoarthritis were given either 3 weekly intra-articular injections of Fermathron plus or saline placebo (van der Weegen et al., 2015). VAS pain, range of motion, and WOMAC pain, stiffness, and function were measured at 1, 3 and 6 months after final injection. Pain and functional scores (WOMAC scale) improved significantly from baseline up to 6 months however HA was not superior to placebo at any follow-up (VAS pain 50m walking from 56.4 to 38.1, p<0.001, and 58.2 to 39.6, p<0.001, respectively). No subgroup analysis resulted in superior outcomes. There were no serious adverse events in either group. Fermathon plus was effective in the management of knee osteoarthritis, and improved knee pain and functional outcome, but was not superior to saline<br><br>In addition, published clinical studies on the equivalent products examined, Hyalgan and Orthovisc, including US studies used in the PMA for each product, confirm that they are safe and effective in achieving their intended use and are comparable in performance to other intra-articular hyaluronic viscosupplements currently available on the market.<br><br>**National surveillance databases**<br>No causal links with the equivalent device Hyalgan or Orthovisc were established for any of the adverse incidents reported on national surveillance databases.<br><br>**Complaints**<br>The complaint rate for Fermathron and Fermathron Plus is very low in proportion to the number of units sold and in comparison with rates reported in the literature for similar products:<br>Fermathron – 7 complaints since January 2015. 3 related to missing variable information on packaging, 1 due to bubbles, 1 due to incorrect Tyvek print and 2 due to inflammation.<br>Fermathron plus - 4 complaints since January 2015. 1 related to units for concentration displayed on labelling and 3 due to inflammation.<br>There have been no product recalls or reportable events. |
| **Acceptability of the benefit/risk profile and side-effects** | The major benefits of viscosupplementation using Fermathron and Fermathron Plus is the relief of pain and stiffness of the knee, hip, ankle and shoulder (Fermathron only) joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the joint and with no other specific complications. The main side effects identified are transient pain and swelling post-injection.<br><br>Given the nature of the benefits, the risks – which are minor and transient – are considered acceptable.<br><br>The IFU describes appropriately the intended use that is supported by sufficient clinical evidence. In addition, it contains all the important |

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| | information to reduce the risk of use error, and on residual risks and their management.<br><br>Overall, the side-effects are acceptable in relation to the product benefits and the device is compliant with the MDD ER6. The benefit/risk profile of Fermathron and Fermathron plus used under normal conditions of use is compatible with a high level of protection of health and safety and in compliance with the MDD ER1. |
| **Conclusion** | A clinical evaluation according to the MEDDEV 2.7.1 Rev 4 was prepared to collect, appraise and analyse clinical data pertaining to Fermathron and Fermathron plus.<br>Sufficient evidence is available to support and demonstrate the performance and safety of Fermathron/Fermathron plus in compliance with the MDD ER1 and MDD ER3.<br>The identified side-effects are acceptable in comparison to the product benefits and Fermathron/Fermathron plus is compliant with the MDD ER6. The benefit/risk profile of Fermathron/Fermathron plus when used as intended is compatible with a high level of protection of health and safety and in compliance with the MDD ER1. |

# 2. SCOPE OF THE CLINICAL EVALUATION

## 2.1 Identification of the device(s)

The Fermathron device family includes Fermathron (product codes 030001 and 030003) and Fermathron plus (product codes 230001, 230005) products, both of which are Class III synovial viscosupplementation medical devices that are approved for the relief of pain and stiffness of the knee, hip, ankle and shoulder (Fermathron only) joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint. Fermathron is also registered under the name Jointlube (030007).

## 2.2 Regulatory scope

This clinical evaluation was prepared according to the MEDDEV 2.7.1 Rev 4 to collect, appraise and analyse clinical data pertaining to the Fermathron device family, including Fermathron and Fermathron plus . An overview of the regulatory status of the devices under consideration is given in Table 6.

**Table 6: Regulatory status of the device(s) under consideration**

| | Fermathron | Fermathron plus |
|---|---|---|
| **Regulatory framework** | ☒ MDD as amended by directive 2007/47/EC<br>☐ AIMDD as amended by directive 207/47/EC | ☒ MDD as amended by directive 2007/47/EC<br>☐ AIMDD as amended by directive 207/47/EC |
| **Legal manufacturer** | Hyaltech Ltd.<br>Starlaw Business Park, Livingston,EH54 8SF<br>United Kingdom<br>Phone: +44 (0) 1506 40 1000 | |
| **Device already CE marked? Since when** | ☒ Yes, since September 1999 (Additional product names Jointlube and Pentavisc, CE marked January 2014)<br>☐ No | ☒ Yes, since June 2008 (Additional product name Kappavisc CE marked at time of original CE marking)<br>☐ No |
| **Device already on the market? Since when?** | ☒ Yes, since September 1999<br>☐ No | ☒ Yes, since June 2008<br>☐ No |
| **Device classification** (acc. Medical Devices Directive 93/42/EEC, Annex IX and MEDDEV 2.4.1 Rev.9) | ☐ I ☐ IIa ☐ IIb<br>☒ III | ☐ I ☐ IIa ☐ IIb<br>☒ III |
| **Regions the device is sold / registered?** | **Fermathron:** Bahrain, Brazil, Europe, Georgia, Jordan, Kuwait, Russia, Saudi Arabia, Turkey, U.A.E., Ukraine | **Fermathron plus:** Bahrain, Europe, Russia, Turkey, U.A.E., Ukraine |

| | | |
|---|---|---|
| | **Fermathron (registered as Jointlube):** Iran, , Kuwait, Turkey | |
| **Sales volumes (correct to 31 December 2017)** | Fermathron (including Jointlube): 2,993,913 units since 2003 | Fermathron plus: 844,357 units since 2009 |

# 2.3 Description of the device(s)

### 2.3.1 General characteristics of the device

Fermathron and Fermathron plus are Class III synovial viscosupplementation medical devices currently approved for the relief of pain and stiffness of the knee, hip, ankle and shoulder (Fermathron only) joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint.

## Fermathron

Fermathron is a clear solution of sterile 1% sodium hyaluronate, molecular weight 1.19 to 2.03 x $10^6$ Daltons, in phosphate buffered saline, contained in a pre-filled syringe for single intra-articular injection into the synovial space of the joint. 2.0 ml of Fermathron viscoelastic is sterilised by filtration and aseptically filled into a sterile, glass, 2.25 ml, single-use syringe. The syringe tip contains a Luer Lok™ fitting to ensure secure of attachment of a needle (not supplied) for injection of Fermathron.

The sterile pre-filled syringe is packed in a tyvek lidded blister pack in an outer cardboard carton, along with a strip of batch identification patient labels and the Instructions for Use leaflet (IFU). The outer surface of the syringe and inside of the blister pack are sterilised by ethylene oxide.

The recommended dosage regimen for patients with mild to moderate osteoarthritis of the knee joint is up to five weekly injections of 2.0 ml into the synovial space of the knee joint. The dosage regimen should be adapted by the Healthcare Professional for injection into the synovial space of the hip, ankle, and shoulder joints. It is recommended that injections in the hip, ankle and shoulder joints are performed using ultrasound or fluoroscopic guidance. The sodium hyaluronate of Fermathron supplements the synovial fluid's natural hyaluronan, which has been depleted by degenerative and traumatic changes to the synovial joint. The duration of effect in patients with mild to moderate osteoarthritis of the knee joint, is up to six months. Duration of effect in the hip, ankle and shoulder joints has not been established by clinical investigation of Fermathron. The performance of Fermathron is due to its biocompatibility and physiochemical properties. The hyaluronan supplements the hyaluronan found naturally in the synovium but which has been depleted by degenerative and traumatic changes to the synovial joint.

## Fermathron plus

Fermathron plus is a clear solution of sterile 1.5% sodium hyaluronate, molecular weight 2.30 to 3.98 x $10^6$ Daltons, in phosphate buffered saline, contained in a pre-filled syringe for single intra-articular injection into the synovial space of the joint. 2.0 ml of Fermathron viscoelastic is sterilised by filtration and aseptically filled into a sterile, glass, 3 ml, single-use syringe. The syringe tip contains a Luer Lok™ fitting to ensure secure of attachment of a needle (not supplied) for injection of Fermathron.

The sterile pre-filled syringe is packed in a tyvek lidded blister pack in an outer cardboard carton, along with a strip of batch identification patient labels and the Instructions for Use leaflet (IFU). The outer surface of the syringe and inside of the blister pack are sterilised by ethylene oxide.

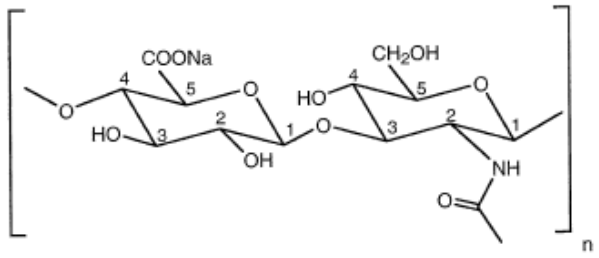
The recommended dosage regimen for patients with mild to moderate osteoarthritis of the knee joint is up to three weekly injections of 2.0 ml into the synovial space of the knee joint. The dosage regimen should be adapted by the Healthcare Professional for injection into the synovial space of the hip and ankle joints. It is recommended that injections in the hip and ankle joints are performed using ultrasound or fluoroscopic guidance. The sodium hyaluronate of Fermathron supplements the synovial fluid's natural hyaluronan, which has been depleted by degenerative and traumatic changes to the synovial joint. The duration of effect in patients with mild to moderate osteoarthritis of the knee joint, is up to six months. Duration of effect in the hip and ankle joints has not been established by clinical investigation of Fermathron plus. The performance of Fermathron is due to its biocompatibility and physiochemical properties. The hyaluronan supplements the hyaluronan found naturally in the synovium but which has been depleted by degenerative and traumatic changes to the synovial joint.

### 2.3.2 Material

The sodium hyaluronate of Fermathron and Fermathron plus is manufactured by biosynthesis using the natural bacterium Streptococcus equi, and is not modified in any way. The sodium hyaluronate has an average molecular weight of 1.19 to 2.03 x $10^6$ Daltons and is dissolved in phosphate buffered saline, providing a pH and osmolality which are biocompatible with synovial fluid.

Sodium hyaluronate is a long chain polysaccharide made up of repeating disaccharide units, units (alternating residues of β-D-(1→3) glucuronic acid and β-D-(1→4)-N-acetylglucosamine), which occurs naturally in the human body. It is particularly abundant in those areas rich in loose connective tissue such as skin, and in the synovial fluid and the eye. At physiological pH, the carboxyl groups are completely dissociated and the polysaccharide is therefore referred to as hyaluronate. Its hydrophilic nature and unique rheological properties allow it to form solutions of high viscosity and elasticity that provide protective, space-filling, shock-absorbing, lubricating and moisturising functions.

Sodium hyaluronate is the sodium salt of hyaluronic acid:




$(C_{14}H_{22}NNaO_{11})_n$

The sodium hyaluronate contained in the Fermathron products is produced through biosynthesis by the naturally occurring bacterium Streptococcus equi (S. equi). The bacterium forms a protective capsule of sodium hyaluronate around itself and it is this capsule that is removed and purified for inclusion in the Fermathron products. The composition of sodium hyaluronate is ubiquitously conserved across all species and the molecule manufactured by Hyaltech Ltd. The sodium hyaluronate from S. equi has been demonstrated to be of the same chemical composition and configuration as sodium hyaluronate from the human umbilical cord and sodium hyaluronate from an avian source (Birmingham_University, 1994).

**Table 5: Composition of Fermathron and Fermathron plus**

| **Parameter** | **Final Product Specification** | |
|---|---|---|
| | **Fermathron** | **Fermathron plus** |
| Sodium Hyaluronate concentration (mg/ml) | 9.75 - 11.0 | 14.0-16.0 |
| Sodium Hyaluronate molecular weight (Daltons) | 1.19 – 2.03 x$10^6$ | 2.30-3.98 x$10^6$ |
| Sodium Chloride concentration (mg/ml) | 7.6 - 9.5 | 6.8-7.6 |
| Phosphates concentration (mg/ml) (Di-sodium hydrogen phosphate and Sodium dihydrogen phosphate) | 0.15 - 0.25 | 0.15 - 0.25 |
| Water for irrigation | q.s. | q.s. |

**Figure 1a**: Fermathron product in blister pack

**Figure 1b:** Fermathron plus product in blister pack

Fermathron and Fermathron plus do not incorporate any medicinal substances, tissues or blood products.

### 2.3.3 Accessories/additional components

Fermathron and Fermathron plus is injected using a sterile needle of an appropriate size. A 19 - 20 gauge needle is recommended for Fermathron whereas an 18-21 gauge needle is recommended for Fermathron plus.

The needle is not supplied in the Fermathron or Fermathron plus product carton. Secure attachment of the needle to the syringe is assured by the Luer Lok™ fitting on the syringe.

### 2.3.4 Packaging and sterilisation

**Fermathron**

Fermathron comprises 2ml of a clear, sterile solution of 10mg/ml sodium hyaluronate, in phosphate buffered saline, pre-filled into a 2.25ml syringe for single intra-articular injection. The sodium hyaluronate solution is sterilised by filtration and is aseptically filled into the sterile, ready to use, disposable glass syringe.

The Fermathron sodium hyaluronate solution in phosphate buffered saline is contained within a sterile clear glass type I borosilicate 2.25 ml syringe barrel with FM27 latex free tip cap and sterile bromobutyl FM257/2 plunger stopper. A clear non-sterile polystyrene plunger rod is fitted to the plunger stopper and a clear non-sterile polypropylene backstop fitted to the syringe barrel. The syringe has a Luer Lok™ fitting to ensure secure attachment of a needle to the syringe. A sterile needle (19 - 20 gauge recommended) that is not supplied in the Fermathron product carton is attached to the tip of the syringe via the Luer Lok™.

During implantation of the sodium hyaluronate viscosupplement solution, the sterile needle contacts the patient and the syringe barrel, tip cap and plunger stopper contact the patient indirectly through contact with the sodium hyaluronate solution. The plunger rod and backstop do not contact the patient.

The pre-filled syringe is packed within a polyvinyl chloride (PVC) blister tray, which is heat sealed with a Tyvek blister lid. The blister pack is sterilised by ethylene oxide, which ensures that the outer surface of

the syringe and the inside of the blister tray are sterile. The sealed blister packed syringe, a product instruction for use leaflet and a strip of patient batch identification labels are packed in a cardboard carton.

**Fermathron plus**

Fermathron plus comprises 2ml of a clear, sterile solution of 15mg/ml sodium hyaluronate, in phosphate buffered saline, pre-filled into a 3ml syringe for intra-articular injection. The sodium hyaluronate solution is sterilised by filtration and is aseptically filled into the sterile, ready to use, disposable glass syringe.

The Fermathron plus sodium hyaluronate solution in phosphate buffered saline is contained within a sterile clear glass type I borosilicate 3.0ml syringe barrel with FM27 latex free tip cap and sterile bromobutyl FM257/2 plunger stopper. A clear non-sterile polystyrene plunger rod is fitted to the plunger stopper and a clear non-sterile polypropylene backstop fitted to the syringe barrel. The syringe has a Luer Lok™ fitting to ensure secure attachment of a needle to the syringe. A sterile needle (18 - 21 gauge recommended) that is not supplied in the Fermathron Plus product carton is attached to the tip of the syringe via the Luer Lok™.

During implantation of the sodium hyaluronate viscosupplement solution, the sterile needle contacts the patient and the syringe barrel, tip cap and plunger stopper contact the patient indirectly through contact with the sodium hyaluronate solution. The plunger rod and backstop do not contact the patient.

The pre-filled syringe is packed within a polyvinyl chloride (PVC) blister tray, which is heat sealed with a Tyvek blister lid. The blister pack is sterilised by ethylene oxide, which ensures that the outer surface of the syringe and the inside of the blister tray are sterile. The sealed blister packed syringe, a product instruction for use leaflet and a strip of patient batch identification labels are packed in a cardboard carton.

Note: Both Fermathron and Fermathron plus previously used a W1883 tip cap, composed of an elastomeric formulation containing 10% rubber. This was discontinued by the syringe manufacturer BDPS and has been replaced by the FM27 tip cap following DEKRA approval of the change (Change Control CR12029).

# 2.4 Technology used

The device under review in this report is based on a technology that has been in existence, with continuous development, for more than 30 years.

## 2.4.1 Fermathron clinical development

The development of Fermathron (1% sodium hyaluronate, molecular weight 1.19 - 2.03 x $10^6$ Daltons, in phosphate buffered saline) was based on the predicate synovial viscosupplementation device, Hyalart (1% sodium hyaluronate, 0.5 - 0.73 x $10^6$ Daltons molecular weight, of avian origin, in phosphate buffered saline). The molecular weight of Fermathron was expressed previously as 0.8 - 1.3 x $10^6$ Daltons, or as an average of 1 x $10^6$ Daltons; see Change Control CR12057. Hyalart, manufactured by Fidia Farmaceutici,

is a device with a closely similar composition and same intended use as Fermathron, and was CE-marked in 1985 for treatment of osteoarthritis of the knee. Hyalart is also known as Hyalgan, e.g. in the U.S. where in 1997, it was the first FDA approved sodium hyaluronate viscosupplement

### 2.4.2 Fermathron plus clinical development

The development of Fermathron plus (1.5% sodium hyaluronate, molecular weight 2.30 to 3.98 x $10^6$ Daltons [previously expressed as 1.46 to 2.42 x $10^6$ Daltons or as an average of 2 x $10^6$ Daltons, see Change Control CR12057], in phosphate buffered saline) was based on the predicate synovial viscosupplementation device Orthovisc, manufactured by Anika Therapeutics Inc., Woburn, Massachusetts, USA, an equivalent device with the same composition (1.5% sodium hyaluronate, 1.0 to 2.9 x $10^6$ Daltons molecular weight, of avian origin, in phosphate buffered saline), and intended use as Fermathron plus.

## 2.5 History of the device

Fermathron was CE marked in accordance with MDD 93/42/EEC on the 8th of September 1999. by the Notified Body MDC and transferred to DEKRA on the 8th of December 2005. On the 2nd of May 2012 the device was additionally CE marked under the product name Jointlube. The product name Pentavisc was added on the 22nd of January 2014 however is no longer used. The name 'Fermathron' will be referenced in this CER to cover all aforementioned product names unless the use of specific products names is appropriate.

Fermathron plus was CE marked in accordance with MDD 93/42/EEC on the 5th of June 2008. The additional product name Kappavisc was CE marked at time of original CE marking however is no longer used. Fermathron Plus is currently distributed by Biomet GmbH.

**Table 6: History of the device**

| Approved date | Version | Description of device modification | Reasons for modifications |
|---|---|---|---|
| 08/09/1999 | N/A | CE marking of Fermathron by NB MDC | N/A |
| 08/12/2005 | N/A | CE marking of Fermathron transferred to NB Dekra | N/A |
| 05/06/2008 | N/A | CE marking of Fermathron plus/ Kappavisc | N/A |
| 02/05/2012 | N/A | Addition Fermathron brand name"Pentavisc" added to CE certificate | N/A |
| 25/10/2013 | N/A | Change to tip cap material from W1883 to FM27 (CR12029) | Manufacturer discontinuation of W1883 material |

# 2.6 Intended purpose and application

The intended purpose and device application are described in Table 7.

**Table 7: Device intended purpose and application**

| | Device Name |
|---|---|
| **Intended purpose** | **Fermathron:** For the relief of pain and stiffness of the knee, hip, ankle and shoulder joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the joint.<br><br>**Fermathron plus:** For the relief of pain and stiffness of the knee, hip and ankle joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the joint. |
| **Medical indication(s)** | The target devices are sterile, single use, surgically invasive devices which are intended to relieve pain and stiffness of the knee, hip, ankle and shoulder joints (Fermathron only) in patients with mild to moderate osteoarthritis. The device is administered using a pre-filled syringe for intra-articular injection into the synovial space of the joint. The device is implantable as it remains in long-term contact and is wholly or mainly absorbed by the body.<br>The device is intended for adult patients only. |
| **Contraindication(s)** | **Contraindications**<br>Do not inject Fermathron/Fermathron plus if the area of the injection is infected or where there is evidence of skin disease. Do not use in patients with known hypersensitivity to sodium hyaluronate.<br>**Incompatibilities**<br>Fermathron/Fermathron plus has not been tested for compatibility with other substances for intra-articular injection. Therefore the mixing or simultaneous administration with other intra-articular injectables is not recommended. |
| **Precautions** | **Special warnings and precautions**<br>Do not use if the sterile packaging has been damaged.<br>Do not use after the expiry date.<br>Sodium hyaluronate is manufactured by fermentation of Streptococcus equi and rigorously purified. However, the physician should consider the immunological and other potential risks that can be associated with the injection of any biological material.<br>Do not use for children.<br>There is no evidence concerning the safety of Fermathron in human pregnancy and lactation. Administration during pregnancy and lactation is at the discretion of the orthopaedic surgeon.<br>Follow national or local guidelines for the safe use and disposal of needles. Obtain prompt medical attention if injury occurs. |

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|---|---|
| | Fermathron/Fermathron plus is a single use device and is intended to be used for a single patient only. If Fermathron/Fermathron plus is used for a second patient the sterility will be compromised and there is a risk of foreign body reaction and/or infection. Fermathron should not be re-sterilised as the device performance may be compromised. Fermathron should be used with a sterile needle that should be discarded after single use. |
| **Name of disease / Condition / Field of Application** | Osteoarthritis resulting from degenerative and traumatic changes to the synovial joint. |
| **Clinical form, stage, severity, symptoms or aspects to be treated** | Mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint. |
| **Target patient population** | Adult patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint. |
| **Target user group** | Healthcare Professionals trained in the technique of intra-articular injections. |
| **Intended application** | ☒ Single-use ☐ Re-usable<br>☒ Invasive ☐ Non invasive<br>☒ Implantable ☐ Non implantable<br>☐ Active ☐ Non active<br>☐ Software |
| **Duration of use or contact with the body** | Long-term surgically invasive device which is wholly or mainly absorbed by the body.<br><br>The bacterial HA of Fermathron is the unmodified native molecule and is identical in structure to that found in the joint, i.e. the molecule is not chemically cross-linked to extend its *in vivo* half-life. The injected (exogenous) HA is therefore readily available for natural metabolic degradation and elimination by the body, with complete metabolisation within a few days (Fakhari and Berkland, 2013). |
| **Maximum number of repeat applications** | The recommended dosage regimen for patients with mild to moderate osteoarthritis of the knee joint is up to five weekly injections of 2.0 ml Fermathron, or up to 3 weekly injections of 2.0 ml Fermathron plus into the synovial space of the knee joint. The dosage regimen should be adapted by the Healthcare Professional for injection into the synovial space of the hip, ankle and shoulder joints (Fermathron only). |
| **Identification of organs, tissues, or body fluids in contact with the device** | The synovial space of the knee, ankle, hip or shoulder (Fermathron only) joint. |

# 2.7 Claims made for the device(s)

The claims intended to be made for the device, on clinical performance and safety are summarized in Table 8.

**Table 8: Claims made for the devices**

| | Performance | Safety |
|---|---|---|
| **Intended use** | For the relief of pain and stiffness of the knee, hip, ankle and shoulder (Fermathron only) joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the joint. | Safe when used as intended |
| **Claims made in available promotional materials** | For the relief of pain and stiffness of the knee, hip, ankle and shoulder (Fermathron only) joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the joint. | Minimal adverse reactions |
| | Increasing mobility | Natural, biocompatible material |
| | Ease of application | |
| | Reduces pain and stiffness in the knee and hip | - |
| | Relieves symptoms for up to 6 months in knee joints | - |
| | Acts primarily mechanically | - |

# 3. CLINICAL BACKGROUND, CURRENT KNOWLEDGE, STATE OF THE ART

## 3.1 Scope

The scope of this section is to discuss the performance and safety of viscosupplements Fermathron and Fermathron plus for the relief of pain and stiffness of the knee, hip, ankle and shoulder (Fermathron only) joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the joint. The objective is to identify in the literature critical factors relating to performance and safety, main complications and side-effects reported, alternatives and current state of the art.

## 3.2 Current Knowledge

The performance of Fermathron and Fermathron plus is due to their biocompatibility and physiochemical properties. The LMW sodium hyaluronate contained in Fermathron and the HMW sodium hyaluronate contained in Fermathron plus is a biopolymer composed of repeating disaccharide units of D-glucuronic acid and N-acetyl-Dglucosamine and though it is biosynthesised by the bacterium Streptococcus equi it has been shown to be the same as the sodium hyaluronate which is found in the human body. The hyaluronan supplements the hyaluronan found naturally in the synovium but which has been depleted by degenerative and traumatic changes to the synovial joint.

Fermathron and Fermathron plus are intended for the relief of pain and stiffness of the knee, hip, ankle and shoulder joints (Fermathron only) in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint. The duration of effect in patients with mild to moderate osteoarthritis of the knee joint is up to six months. Duration of effect in the hip, ankle and shoulder joints has not been demonstrated.

### 3.2.1 Viscosupplementation with Intra-articular Injection of Hyaluronan - Mechanism of action and therapeutic benefits

Exogenous linear hyaluronan supplied to the joint via intra-articular injections can be cleared from osteoarthritic joints in less than a day, or from 1.5 to 9 days for chemically cross-linked hyaluronan (Juni et al., 2007), and despite a short course of weekly intra-articular injections being the normal treatment regimen, the therapeutic benefits of viscosupplementation have been shown to last much longer, usually from 3 to 6 months. Whilst the principle intended purpose of introducing exogenous hyaluronan into the

synovial joint is to relieve pain through lubrication and cushioning, a number of in vitro and in vivo studies have focussed on assessing the cellular level mechanisms of action and possible disease-modifying effects of hyaluronan viscosupplementation on the osteoarthritic synovial joint, in an attempt to explain the longer-term clinical physiological benefits in pain reduction and functional improvement. Intra-articular hyaluronan treatments are postulated to promote healing and repair (e.g. stimulation of chondrocyte growth and metabolism, and stimulation of production of articular cartilage matrix components), inhibit destruction (e.g. inhibition of chondro-degradative enzymes and matrix-destructive inflammatory processes) (Cianflocco, 2013; McNeil, 2011), and to have anti-inflammatory and analgesic effects, i.e. a direct protective action on nociceptive nerve endings (Frampton, 2010).

Viscosupplementation by intra-articular injection of exogenous HA attempts to restore the normal biomechanical and physiological functions of pathologically altered synovial fluid (Ayhan *et al.*, 2014; Evaniew *et al.*, 2014). A systematic non-clinical review of the scientific literature by Altman *et al.* (2015) summarises the current thinking on the mechanisms of viscosupplementation action. They conclude that there is evidence for numerous concurrent mechanisms in which intra-articular HA may provide clinical benefit in knee osteoarthritis. Although the precise *in vivo* mechanisms of action are still not known, several studies suggest that along with restoring elasticity and lubricity to synovial fluid, viscosupplements have disease-modifying and chondroprotective effects through a reduction of synovial inflammation, promotion of endogenous HA and proteoglycan production, and altered behaviour of immune cells (Altman *et al.*, 2015; Li *et al.*, 2012a; McArthur *et al.*, 2012; Mladenovic *et al.*, 2014; Oliveira *et al.*, 2014; Ozkan *et al.*, 2015; Strand *et al.*, 2015).

HA has indirect and direct analgesic activity within the joints: indirect effect is via the anti-inflammatory properties of HA; direct effect is by inhibition of nociceptors and the decreased synthesis of bradykinin and substance P. The results of Caires *et al.* (2015) show that healthy HA antagonises TRPV1 (polymodal transient receptor potential vanilloid subtype 1 channels) activity and significantly decreases nociceptor excitability, thus adding an additional mechanistic explanation to the anti-nociceptive effects of intra-articular HA injections. A study by Xu *et al.* (2015) has demonstrated that dysregulation in microRNAs in synovial fluid from patients with knee osteoarthritis, and their affected biologic cellular processes, might play an important role in osteoarthritis pathogenesis and HA- mediated therapeutics.

# 3.3 State of the Art

### Autologus Conditioned Serum (ACS)

The therapeutic use of interleukin 1 (IL-1) cytokine receptor antagonists (IL-1RA) has promoted the development of new biological therapies for osteoarthritis (OA). Autologous conditioned serum (ACS) is an alternative, safe and well-tolerated treatment in OA. Autologus conditioned serum is created by the incubation of venous blood with glass beads for 24 hours at 37ºC, after which the blood is recovered and centrifuged (Demange et al, 2014). ACS, containing endogenous anti-inflammatory cytokines including IL-1RA and several growth factors, could reduce pain and increase function and mobility in mild to moderate knee OA. Given the limited data available on the composition of ACS, the mechanisms through which ACS produces clinical improvement, the duration of its effect and the changes in cytokine levels after repeated injections are still unknown and further investigation is required.

### Platelet Rich Plasma (PRP)

The use of Platelet Rich Plasma is another treatment option for OA and achieves its function by delivering a high concentration of growth factors directly to the affected joint, potentially resulting in an increase in chondrocytes and subsequent hyaluronic acid production. PRP may also affect pain by inhibiting the action of inflammatory cytokines such as IL-1 and NHkB (Demange et al, 2014). A large RCT studying the efficacy of PRP treatment stated there was an overall benefit to using the treatment, however further investigation was deemed necessary (Cohen et al, 2015).

Clinical studies to date are difficult to compare due to variation in PRP compositions and differing effects on inflammation (Evans et al, 2014)

Filardo et all , 2015 compared PRP with Hyaluronic acid in a study including 192 patients. Two patients reported severe pain and swelling after HA injections, while no major adverse events were noted in the PRP group. However, PRP presented overall significantly more post injection swelling and pain. Both treatments proved to be effective in improving knee functional status and reducing symptoms: the IKDC score in the PRP group rose from 52.4 ± 14.1 to 66.2 ± 16.7 at 12 months ($P < .0005$), and in the HA group it rose from 49.6 ± 13.0 to 64.2 ± 18.0 at 12 months ($P < .0005$). A similar trend was observed for all the clinical scores used. The comparative analysis of the 2 treatments showed no significant intergroup difference at any follow-up evaluation in any of the clinical scores adopted. The authors concluded that PRP does not provide a superior clinical improvement with respect to HA, and therefore it should not be preferred to viscosupplementation as injective treatment of patients affected by knee cartilage degeneration and OA.

A study by Di Sante et al reported in 2016 concluded that in circumstances of severe hip osteoarthritis Intra-articular PRP had an immediate effect on pain that was not maintained at longer term follow-up when, on the contrary, the effects of intra-articular HA were evident.

### Lubricants and Viscosupplementation

Developments taking place in the formulation of HA viscosupplements include modifying the formula to increase the duration of action within the affected joint. Cross-linking of HA have been shown to increase product half-life by resulting in a more viscous, gelatinous solution which the body finds harder to metabolise (Demange et al, 2014)

### Growth Factor Related Injections

Current research into cytokine cascades and their subsequent effect on OA pathology is leading development into new forms of intra-articular injections. Growth factors including IGF-1, TGF-β, FGF-18 and inflammatory cytokines such as IL-4, IL-10, PGDF and adrenomedullin are currently involved in the advance of new treatments. The cytokine IGF-1 is considered anabolic to chondrocytes, subsequently stimulating matrix formulation and cell growth (Demange et al., 2014). Studies are currently in the pre-clinical phase which may lead to in-man studies in the near future.

### Gene Therapy

Gene therapy in the treatment of OA involves local gene transfer to the affected joint, allowing a sustained therapeutic dose of gene product to remain within the affected area. The treatment can be achieved using cells genetically modified in vivo or by utilizing a viral or non-viral vector. Intra-articular gene therapy has been evaluated in phase I clinical trials in patients with RA and OA. A phase II trials are currently underway using allogenic cells expressing transforming growth factor β1. (Evans et al.,2014)

### Cell Based Therapies

The greatest activity in relation to developing new cell-based OA treatments surrounds the use of mesenchymal stem cells (MSCs). Bone marrow mesenchymal stem cells (BM-MSC's) are multipotent stem/stromal cells that can differentiate into a variety of cell types, including: osteoblasts, chondrocytes, myocytes and adipocytes (Demange et al, 2014). BM-MSCs can be derived from adult or embryonic tissues.

As mesenchymal stem cells are autologous, the risk of rejection is negated. Furthermore, it is possible to retrieve high numbers of good quality cells which is highly advantageous for successful differentiation into the necessary tissues required in the OA affected joint (Richards et al, 2016) The use of BM-MSCs has increased hugely in the past 3 years: 31 trials have been undertaken; 23 of them involve MSCs and, of these, 20 were registered on ClinicalTrials.gov from 2010 onwards. Encouraging preclinical data have emerged in relation to preventing post-traumatic OA, regenerating damaged cartilaginous surfaces and reducing pain. (Evans 2014).

# 3.4 Applicable standards and guidance documents

BS EN ISO 14630:2012 Non-active surgical implants – General requirements

# 3.5 Natural course of the medical condition

Osteoarthritis (OA) is a degenerative disease characterised by joint pain and progressive dysfunction, resulting from destruction of the articular cartilage and changes in the subchondral bone, with occurrences of joint space narrowing, inflammation/synovitis, and periarticular osteophyte formation, as well as degeneration of ligaments and menisci (Ammar et al., 2015; Ayhan et al., 2014). Rather than being a simple process of "wear and tear", osteoarthritis is a complex disease with multifactorial etiopathogenesis, driven by proinflammatory cytokines and proteolytic molecules within the affected joint (Ayhan et al., 2014; Kohlhof et al., 2016; Pintan et al., 2014).

The main proinflammatory cytokines involved in the pathophysiology of OA are interleukin (IL)-1β, tumour necrosis factor (TNF), and IL-6 (Chang et al., 2012; Pintan et al., 2014). These cytokines act through several mechanisms contributing to the phenotype shift of chondrocytes, through which activated cells increase the expression of catabolic and proinflammatory genes. In addition, these cytokines intensify and maintain osteoarthritic disease by inducing the production of other proinflammatory cytokines, such as IL-8, IL-15, IL-17, IL-8, IL-21, and leukemia inhibitory factor. The inflammatory microenvironment supports the rise of proteolytic enzymes, e.g. matrix metalloproteinases (MMP-1, MMP-3, and MMP-13). During cartilage degradation, fragments of matrix components are released, such as aggrecan, collagen, and fibromodulin fragments, which maintain inflammatory cytokine production. Furthermore, oxide synthase 2, cyclooxygenase (COX)-2, and prostaglandin E gene expression are increased, contributing to articular inflammation and destruction by enhancing the activation and production of MMPs and the inhibition of type II collagen proteoglycan synthesis.

Osteoarthritis is the most common joint disorder and a major cause of disability; it is estimated that 10–15% of the worldwide population over 60 has some degree of osteoarthritis (Kohlhof et al., 2016). Among the major joints, the knees are the ones most affected, such that knee osteoarthrosis gives rise to functional deficits in 10% of individuals over the age of 55 years and in 25% in cases of advanced disease. Patients affected by osteoarthritis suffer from pain, limitations of movement, and ultimately loss of joint function.

The Kellgren and Lawrence system is a common method of classifying the severity of knee osteoarthritis (OA) using five grades from 0 (none) to 4 (severe). This classification was proposed by Kellgren et al. in 1957 and later accepted by WHO in 1961. It measures the presence of typical features of osteoarthritis:

Joint space narrowing - bone is visible on x-ray but the articular cartilage that covers it is not. A normal joint therefore appears to have a space between the bones. Any decrease in space implies a reduction in cartilage cover.

Osteophytes - small bony projections that form around joint margins. Thought to be a result of the body trying to increase joint surface area to decrease pressure. They are responsible for limiting range of motion and can cause pain.

Sclerosis - this means 'hardening' and is a sign of osteoarthritis, seen as increased white areas in the bone at the joint margins.

| Grade | Description |
|---|---|
| 0 | No radiographic features of osteoarthritis |
| 1 | Possible joint space narrowing (normal joint space is at least 2 mm at the superior acetabulum) and osteophyte formation |
| 2 | Definite osteophyte formation with possible joint space narrowing |
| 3 | Multiple osteophytes, definite joint space narrowing, sclerosis and possible bony deformity |
| 4 | Large osteophytes, marked joint space narrowing, severe sclerosis and definite bony deformity |

Although widely used, limitations of the system include inconsistencies in interpretation in subsequent studies as well as lack of recognition of patellofemoral arthritis as a distinct or contributory radiographic factor.

**Role of Endogenous Hyaluronan in the Synovial Joint**

HA is a naturally-occurring, high-molar-mass, uniform, linear, unbranched, non-sulphated glycosaminoglycan comprising repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine, identical in chemical structure across all vertebrate and streptococcal species (Ahn et al., 2012; Ballin et al., 2013; Bogdan Allemann and Baumann, 2008). It is found not only in joints, but throughout the body in all connective tissue, the skin, interstitial membranes, the vitreous body of the eye, umbilical cord, and the cumulus cell matrix that surrounds oocytes prior to ovulation (Balazs, 2009; Bergeret-Galley, 2004; Boeriu et al., 2013; Medina et al., 2012; Sakai et al., 2000; Tammi et al., 1988), and has diverse biological functions (Dicker et al., 2014). The molecular weight of HA is polydisperse and usually in the range of 4 to 7 x $10^6$ Daltons in healthy adults, with the majority of molecules greater than 4 x $10^6$ Daltons (Balazs and Denlinger, 1993; Hui et al., 2012). As HA exhibits no species or tissue specificity (Flynn et al., 2011), the molecule is inherently non-immunogenic (Agerup et al., 2005; Gold, 2009; Gold, 2007) and therefore highly biocompatible.

The synovial joint is a complex biological system containing synovial fluid within a cavity bounded by articular cartilage and synovium. The synovial fluid, normally a clear, straw-coloured viscous liquid, is secreted into the joint cavity by the synovium. Lubrication of healthy joints is provided by the interplay of articular cartilage at the bone ends in combination with the synovial fluid in between; this composition yields remarkably low friction and low wear during joint articulation (Kohlhof et al., 2016). The synovial fluid volume is approximately 2ml in normal human knee joints and contains electrolytes, low molecular weight organic molecules, macromolecules such as glycosaminoglycans (2% chondroitin-4-sulphate, 98% HA) and proteoglycan 4 (PRG4, also known as lubricin) (Fakhari and Berkland, 2013; Hui et al., 2012). The

molecular and cellular constituents within synovial fluid give rise to its unique properties and functions (lubrication, metabolic, and regulatory) in maintaining joint homeostasis. HA is one of the main constituents of synovial fluid and cartilage matrix, and is synthesised and secreted by chondrocytes and fibroblast-like (type B) synoviocytes lining the joint cavity (Axe et al., 2013; Ayhan et al., 2014; Juranek et al., 2014; McArthur et al., 2012). HA is produced in large quantities, leading to the formation of extensive macromolecular entanglements and networks conferring on the synovial fluid its characteristic rheological properties, i.e. the elasticity and viscosity responsible for shock absorption under conditions of high compression or shear, and lubrication in low load states (Guidolin and Franceschi, 2014).

HA is present in concentrations of between 2.5 and 4 mg/ml in normal human synovial fluid (Balazs et al., 1967; Balazs and Denlinger, 1993; Dahl et al., 1985; Kosinska et al., 2015; Park et al., 2014; Saari and Konttinen, 1989), whereas the mean concentration from patients with osteoarthritis is reduced and ranges from approximately 1.2 to 2.2 mg/ml (Hui et al., 2012; Kosinska et al., 2015); this reduction is due to exudation from the joint and/or decreased production by synoviocytes (Cianflocco, 2013). The average molecular weight of HA in normal synovial fluid is 5 to 7 x $10^6$ Daltons (Cianflocco, 2013). It is well established that synovial fluid HA lubricates the various synovial joints of the body (Corvelli et al., 2015), provides a protective coating for articular cartilage, acts as a shock absorber, and gives mechanical stability to the collagen network (Conduah et al., 2009; Goldberg and Goldberg, 2010). HA enhances the viscoelastic nature of synovial fluid: viscosity increases with slow movements, enabling the HA to behave like a lubricant, whereas with high shear, rapid motion, HA acts like a shock absorber; this adaptive, "pseudoplastic" (non-Newtonian) ability reduces stress on cartilage and friction between surface tissues (Axe et al., 2013; Ayhan et al., 2014; Fakhari and Berkland, 2013). Furthermore, HA anchored at the outer surface of articular cartilage by lubricin molecules, complexes with joint phosphatidylcholines as part of the extreme hydration–lubrication mechanism of synovial joints (Seror et al., 2012). HA molecules restrict the entry of large plasma proteins and cells into the aqueous phase of synovial fluid, they facilitate the transport of water and small solutes through the synovial fluid to the articular cartilage from capillaries in the synovium, and they reduce fluid loss as intra-articular pressure is raised during joint flexion (Guidolin and Franceschi, 2014). HA also forms the backbone for the proteoglycans of the extracellular matrix, and functions through anti-inflammatory (Vincent et al., 2013), analgesic (Caires et al., 2015; Rivera, 2016), anabolic, and chondroprotective mechanisms. HA therefore plays a central role in maintaining the physiological internal environment of the joint.

In the osteoarthritic joint, elevated synovial fluid levels of free radicals, inflammatory cytokines, and proteolytic enzymes adversely affect the metabolism of the synovium type B fibroblasts, leading to biosynthesis of HA of reduced molecular weight, as has been shown by analysis of synovial fluid from pathologic joints (Guidolin and Franceschi, 2014; Kosinska et al., 2015). In addition, HA also may be depolymerised by oxygen-derived free radicals and intracellularly by hyaluronidases, and other glycosidases from synoviocytes and leukocytes in the synovium. The decline in HA molecular size is coupled with dilution by infiltration of plasma fluid and proteins; synovial inflammation causes increased synovial membrane permeability (Ayhan et al., 2014). The reduced concentration and molecular weight of HA alters its rheological properties and impairs the molecule's function (resulting in diminished viscosity and reduced capacity to absorb shock and provide lubrication), and contributes to the progression of

osteoarthritis through cartilage damage and increased symptoms (Ammar et al., 2015; Evaniew et al., 2014; McArthur et al., 2012).

# 3.6 Available therapeutic options

The treatment of osteoarthritis is multi-modal and includes non-pharmacological interventions such as patient education, physical therapy, weight loss, low-impact exercises, and extra-articular devices for functional assistance (Cianflocco, 2013). Pharmacological treatment options, aimed at pain relief, typically include analgesics such as acetaminophen (paracetamol), oral non-steroidal anti-inflammatory drugs (NSAIDs), topical NSAIDs, and intra-articular corticosteroid injections. Opioid and non-narcotic analgesics may be prescribed in patients with refractory pain.

In a review by Bruyere (2014) ESCEO assembled a task force of 13 international experts on osteoarthritis and its various treatments including rheumatologists, clinical epidemiologists, and clinical scientists. Existing guidelines were reviewed; all interventions listed and recent evidence were retrieved using established databases. A schematic flow chart showing the treatment algorithm reached after many rounds of consultation can be seen overleaf in figure 2. This details the many treatment options for knee OA which are discussed further below. Furthermore an evaluation of OARSI guidelines for the non-surgical management of knee OA (McAlindon et al. 2014) also discussed some additional treatment options for knee and multi-joint OA which are also detailed below.

**Core principles of treatment**

Information access and education on OA for the patient on disease progression and available treatment options. This should include alteration of lifestyle behaviours that may reduce OA symptoms.

Weight loss, if required, is shown to reduce OA symptoms.

Exercise and physical activity has been shown to be effective on pain and function of OA affected joints. Muscle strengthening exercises for the quadriceps and aerobic exercises such as swimming and walking are highly recommended.

**Non-pharmacological background treatment**

Knee braces/ shoe insoles to prevent malalignment (knee only)

Physical therapy

Walking aids

Thermal agents (including ultrasound)

Manual therapy

Patellar taping (knee only)

Chinese acupuncture

Transcutaneous Electric Nerve Stimulation (TENS)

Balneotherapy/spa therapy

Monticone et al , 2016 studied HA injections vs physical therapy and HA injections in conjunction with physical therapy. They state that physical therapy agents seemed to have greater effects than intra-articular viscosupplementation on disability and pain. In the other cases both intra-articular viscosupplementation and physical and rehabilitative interventions seemed to be equally effective in improving disability, pain, and quality of life in subjects with knee and ankle OA .

**Pharmacological background treatment**

**Paracetamol**

Paracetamol is recommended at doses no greater than 4g/day as an initial analgesic treatment approach, adverse effects are rare and it is generally a well tolerated drug, particularly for musculoskeletal pain (Abdulla et al, 2013). However, some studies have shown that paracetamol has a minimal effect on symptoms and is associated with an increased risk of gastrointestinal adverse events (Bruyere et al, 2014).

**Chronic Symptomatic Slow Acting Drugs for Osteoarthritis (SYSADOA)**

Chronic Symptomatic Slow Acting Drugs for Osteoarthritis (SYSADOA) include glucosamine sulphate and/or chondroitin sulphate. Both drugs are often used in combination as dietary supplements which may offer similar benefits on joint structure changes in patients with mild-to-moderate disease. Avocado soybean unsafonifiables (ASU) and diacerein are also considered SYSADOA but have limited clinical evidence supporting their efficacy. Strontium ranelate (SR) which was originally used for postmenopausal osteoporosis and osteoporosis in males, has been shown to have a positive effect on subchondral bone and cartilage and subsequent OA disease progression. However the possibility of increased cardiovascular risks means that further investigations are required (Bruyere et al, 2014).

**Topical NSAIDs**

Topical Non-steroidal anti-inflammatory drugs (NSAIDS) have been shown to have a moderate effect on OA pain, with better gastrointestinal safety than oral NSAIDS (Bruyere et al, 2014; Abdulla et al, 2013)

**Topical Capsaicin**

Capsaicin is the active ingredient in chili peppers and is mainly used for nerve pain but has found to be useful in the treatment of OA related pain. (Cohen et al. 2015) The main adverse effect is a burning sensation at the site of application (Abdulla et al. 2013)

### Advanced Pharmacological treatment

### Oral NSAIDs

Oral NSAIDs are shown to provide better analgesia than paracetamol in the treatment of OA and are appropriate for patients experiencing higher levels of pain (Abdulla et al, 2013). NSAIDs can also be effective when SYSADOA have failed to provide adequate results, or can be used in combination to optimise pain relief (Bruyere et al, 2014). Recent short-term clinical trials have shown no significant difference in the efficacy between COX-2 selective, partially selective and non-selective NSAIDs. However, NSAIDs are associated with gastrointestinal problems and often require an accompanying prescription of proton pump inhibitor (PPI) to decrease this risk (Bruyere et al, 2014). Increased risk of serious cardiovascular events are also associated with NSAID use including diclofenac, coxibs and ibuprofen but not with naproxen. For this reason coxibs or high dose diclofenac or ibuprofen should be avoided in patients at high risk of major cardiovascular events. Oral NSAIDs can also have a negative effect on renal function, particularly in the elderly, causing fluid retention, odema and worsening of congestive heart failure (Abdulla et al, 2013).

### Intra-articular Hyaluronic Acid Injection

HA products are divided into two major types, native (linear) and cross-linked. Native HA products are injected 3 to 5 times per treatment course. Cross-linked HA was developed more recently and products are generally given as a single injection. The advantages of linear HA injection are a safety profile established based on the results of longer-term clinical use and that repeat visits during the treatment course allow monitoring of the patient. Cross-linked HA is advantageous in that only a single injection is needed to achieve the same duration of effect. The cross-linking results in a greater resistance to degradation and therefore a longer residence time in the body, thus reducing the general risks associated with intra—articular injections.

HA product efficacy may be affected by OA phenotype. OA characteristics vary from patient to patient and HA is not indicated in severe OA. In the knee, it has been reported that HA injection is more effective in femorotibial than femoropatellar OA. In acute inflammation with severe effusion, efficacy of HA may be impaired due to enzymes and oxidants (hyaluronidases, free radicals) degrading the HA chains. (Legre-Boyer 2015).

Refer to section 3.2 for further information.

### Intra-articular Corticosteroid Injection

Intra-articular Corticosteroid injections involve the injection of e.g. methylprednisolone acetate or triamcinoclone hexacetonide into the affected joint and have been shown to have a higher efficacy than IA-HA in the first few weeks post-injection but have limited duration of effect (Bruyere, 2014). Several randomized controlled trials have demonstrated short-term effectiveness of corticosteroid injections in the treatment of OA, particularly in the knee. Whilst meta-analyses suggested there may also be a significant long-term benefit between 16-24 weeks, however this may require the administration of higher doses of corticosteroids (Abdulla et al, 2013).

A meta- analysis conducted and reported by Bannuru RR, Schmid CH et al in 2015 compared the effectiveness of pharmacologic interventions for knee osteoarthritis. The study reviewed Randomized trials of adults with knee OA comparing 2 or more of the following: acetaminophen, diclofenac, ibuprofen, naproxen, celecoxib, intra-articular (IA) corticosteroids, IA hyaluronic acid, oral placebo, and IA placebo. They concluded that Intra-articular treatments were superior to nonsteroidal anti-inflammatory drugs, possibly because of the integrated IA placebo effect. Small but robust differences were observed between active treatments. All treatments except acetaminophen showed clinically significant improvement from baseline pain

**Pharmacological attempts before surgery**

**Short term weak opioids**

The use of tramadol has been shown to be effective in pain-relief and increasing function however adverse events often lead to withdrawal of the drug from the patient. Combination therapy using tramadol and paracetamol in adjunct with NSAIDs is often successful in patients who have not responded to treatment with NSAIDs alone (Bruyere et al, 2014)

**Anti-depressants**

Anti-depressants are often prescribed in pain management as they centrally alter the pain neurotransmitters serotonin and norepinephrine, which may be beneficial to OA associated discomfort. Duloxetine was shown to improve knee pain in patients who had not responded to NSAIDs in a short-study, however these effects need to be balanced against the potential side-effects of the drug including nausea, fatigue, dry mouth and constipation (Bruyere et al, 2014).

**End-stage disease management and surgery**

**Total Joint Replacement (TJR)**

Total joint replacement in the knee has been shown to be very effective in relieving the symptoms of OA, with a high benefit/risk ratio when patients are well selected, fully informed and undertake suitable physical therapy post-surgery. 95% of all total joint replacement prostheses for the knee remain viable 20 years post-implantation with only 20% of patients finding the procedure unsuccessful (Bruyere, 2014). Recipients of this surgery can return to normal activities 6-12 weeks provided an adequate rehabilitation program is followed. Hip joint replacement is also widely recommended for end-stage symptomatic OA patients (Nelson et al, 2014)

### Unicompartmental knee replacement or arthroplasty

During knee replacement surgery, damaged bone and cartilage is resurfaced with metal and plastic components. In unicompartmental knee replacement (also called "partial" knee replacement) only a portion of the knee is resurfaced. This procedure is an alternative to total knee replacement for patients whose disease is limited to just one area of the knee.

Because a partial knee replacement is done through a smaller incision, patients usually spend less time in the hospital and return to normal activities sooner than total knee replacement patients. (Bruyere, 2014)

### Classical oral or transdermal opioids

Opioid analgesics are indicated in patients with severe symptoms who are unable or unwilling to receive surgery. Opioid use in older people may pose less risk than NSAIDs which are associated with a number of side-effects which are more pronounced in the elderly population (Abdulla et al, 2013)

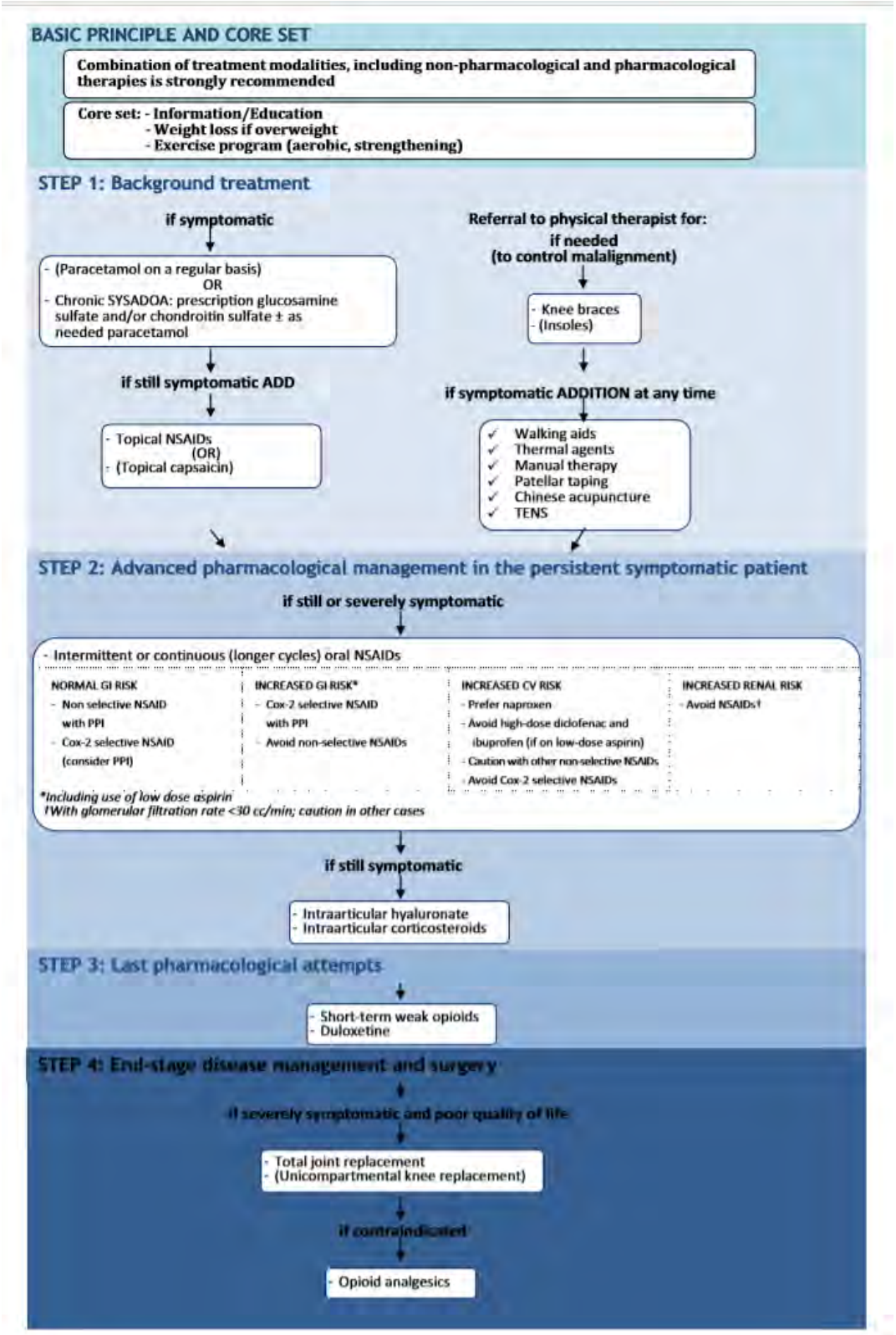



Figure 2: A proposed algorithm recommendation for the management of knee osteoarthritis in Europe and Internationally: A report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) (Bruyere et al., 2014)

# 3.7 Hazards due to used substances and technology

The risk analysis for Fermathron and Fermathron plus was performed in accordance with ISO 14971/EN ISO 14971 'Medical Devices – Application of Risk Management to Medical Devices' to identify characteristics related to the safety of the device within the context of its intended use, and potential hazards arising from the device or its use. All risks have been mitigated to an acceptable level. No new risks were identified from either the literature search or from materiovigilance of equivalent devices.

## Anticipated adverse device effects

There are few risks associated with the use of Fermathron and Fermathron plus, the materials used in the manufacture of these products is fully biocompatible and do not cause any specific hazards. Intra-articular hyaluronic acid injections have a good safety record and have been in clinical use for over 30 years. Adverse reactions are rare however injection site pain and swelling are known and expected complications which usually disappear after 2-3 days. Prevalence is reported as 2-6% in the knee. Rarely, acute inflammatory reactions with a pseudoseptic aspect may occur (1-2%). (Legré-Boyer 2015).

The Fermathron and Fermathron plus IFU states the following:

**Adverse reactions**

Transient pain and swelling may occur following intra-articular injections.

Rarely an inflammatory reaction could occur which may or may not be associated with Fermathron / Fermathron plus

There is little morbidity associated with IA-HA injections, with a reported infection rate of between 1 in 3000 to 1 in 50,000 being reported in the literature (Evans et al, 2014). Despite this relatively low infection rate, there is obviously an increased cumulative risk in repeat injections into the affected area. However this risk is minimised by the trained healthcare professional administering the treatment, by following aseptic technique as recommend in the Fermathron and Fermathron plus IFUs.

## Possible interactions with concomitant medical treatments

As stated in the Fermathron and Fermathron plus IFU neither device has been tested for compatibility with other substances for intra-articular injection. Therefore the mixing or simultaneous administration with other intra-articular injectables is not recommended.

# 4. DEVICES UNDER EVALUATION

## 4.1 Type of evaluation

The present clinical evaluation is based on clinical investigations, the scientific literature currently available, and supporting evidence from equivalent products.

## 4.2 Demonstration of equivalence

### 4.1.1 Identified equivalent device(s)

Hyaltech has identified the following predicate devices equivalent to Fermathron and Fermathron plus:

**Fermathron:**

The predicate device to which equivalence was drawn during the development of Fermathron was Hyalart (1% low molecular weight sodium hyaluronate (0.5 - 0.73 x $10^6$ Daltons) of avian origin, in phosphate buffered saline), manufactured by Fidia Farmaceutici S.p.A., Italy on behalf of Bayer AG. Hyalart is also known as Hyalgan, e.g. in the U.S. where in 1997, it was the first FDA approved sodium hyaluronate viscosupplement.

**Fermathron plus:**

The predicate device to which equivalence was drawn during the development of Fermathron Plus is Orthovisc (1.5% sodium hyaluronate 1.0 - 2.9 x $10^6$ Daltons molecular weight of bacterial origin, in phosphate buffered saline). Orthovisc is manufactured by Anika Therapeutics, Woburn, Massachusetts, USA. Orthovisc was first approved in the U.S. in 2004.

### 4.1.2 Comparison of clinical, biological and technical characteristics

The clinical, biological and technical properties of Fermathron and Fermathron Plus and their equivalent devices are summarized in Table 7a and Table 7b.

The following sources of information were used to gather as much reliable information as possible on Hyalgan and Orthovisc:

https://hyalgan.com/wp-content/themes/Nebula-master/pdf/hyalgan_pi.pdf

https://www.accessdata.fda.gov/cdrh_docs/pdf/P950027a.pdf

http://orthovisc.cz/wp-content/uploads/2017/04/OV013_Orthovisc_IFU_AML500-271C.pdf

https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030019b.pdf

## Table 7a: Comparative table of Fermathron and Hyalart (also known as Hyalgan)

| | | **Device under evaluation:** | **Equivalent model:** | **Evaluation whether the difference can have a significant clinical impact** |
|---|---|---|---|---|
| **Device name** | | **Fermathron** | **Hyalart (Europe)**<br>**Hyalgan (USA)** | N/A |
| **Legal manufacturer** | | **Hyaltech** | **Fidia Farmaceutici** | N/A |
| **Relationship to the device** | | Legal manufacturer | Legal manufacturer | N/A |
| **Regulatory status** | | CE marked September 1999 | CE marked 1987<br>PMA P950027 approved 28th May 1997 | N/A |
| **Illustration** | |  |  | N/A |
| **Intended purpose** | IFU reference | 032-45-K5<br>Revised 01/2015 | Hyalgan® IFU<br>Revised May 2014<br>https://hyalgan.com/wp-content/themes/Nebula-master/pdf/hyalgan_pi.pdf | N/A |
| | Indication(s) | For the relief of pain and stiffness of the **knee, hip, ankle** and **shoulder joints** in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint. | Hyalgan is indicated for the treatment of pain in osteoarthritis (OA) of the **knee** in patients who have failed to respond adequately to conservative nonpharmacologic therapy, and to simple analgesics, e.g., acetaminophen. | Equivalent intended use however Fermathron has a wider range of applications |
| | Contraindication(s) | - Do not inject Fermathron if the area of the injection is infected or where there is evidence of skin disease.<br>- Do not use in patients with known hypersensitivity to sodium hyaluronate. | - Do not administer to patients with known hypersensitivity to hyaluronate preparations.<br>- Intra-articular injections are contraindicated in cases of present infections or skin diseases in the area of the injection site to | Equivalent Contraindications. Not significant |

| | | Device under evaluation: | Equivalent model: | Evaluation whether the difference can have a significant clinical impact |
|---|---|---|---|---|
| | | | reduce the potential for developing sceptic arthritis. | |
| | Warnings and precautions | - Do not use if the sterile packaging has been damaged.<br>- Do not use after the expiry date. | - Do not use Hyalgan if the package is opened or damaged. Store in the original packaging (protected from light) below 77ºF (25ºC). DO NOT FREEZE. | Not significant |
| | | - Sodium hyaluronate is manufactured by fermentation of Streptococcus equi and rigorously purified. However, the physician should consider the immunological and other potential risks that can be associated with the injection of any biological material. | - Use caution when injecting Hyalgan into patients who are allergic to avian proteins, feathers, and egg products.<br>- Anaphylactoid and allergic reactions have been reported with this product. See Adverse events section for more detail. | Not significant. Fermathron does not contain material of avian origin therefore precaution relating to this does not apply. |
| | | - Do not use for children. | The safety and effectiveness if Hyalgan have not been demonstrated in children. | Not significant. |
| | | - There is no evidence concerning the safety of Fermathron in human pregnancy and lactation. Administration during pregnancy and lactation is at the discretion of the orthopaedic surgeon. | The safety and effectiveness if Hyalgan have not been demonstrated in pregnant women.<br>The safety and effectiveness if Hyalgan have not been demonstrated in lactating women. | Not significant |
| | | - Follow national or local guidelines for the safe use and disposal of needles. Obtain prompt medical attention if injury occurs. | N/A | Not significant |
| | | - Fermathron is a single use device and is intended to be used for a single patient only. If Fermathron is used for a second patient the sterility will be compromised and there is a risk of foreign body reaction and/or infection. | - Strict aseptic administration technique must be followed to avoid infections in the injections site. The vial/syringe is intended for single use. | Not significant |

| | | Device under evaluation: | Equivalent model: | Evaluation whether the difference can have a significant clinical impact |
|---|---|---|---|---|
| | | - Fermathron should not be re-sterilised as the device performance may be compromised.<br>- Fermathron should be used with a sterile needle that should be discarded after single use. | - STERILE CONTENTS. The vial/syringe is intended for single use. The contents of the vial/syringe must be used immediately once the container has been opened. Discard any unused Hyalgan. | Not significant |
| | | **Incompatibilities**<br>Fermathron has not been tested for compatibility with other substances for intra-articular injection. Therefore the mixing or simultaneous administration with other intra-articular injectables is not recommended. | - Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronic acid can precipitate in their presence.<br>- The safety and effectiveness of the use of Hyalgan concomitantly with other intra-articular injectables have not been established. | Not significant |
| | | **Adverse reactions**<br>Transient pain and swelling may occur following intra-articular injections.<br>Rarely an inflammatory reaction, septic arthritis, or arthralgia could occur which may or may not be associated with Fermathron. | - Transient increases in inflammation in the injected knee following Hyalgan injection in some patients with inflammatory arthritis such as rheumatoid arthritis or gouty arthritis have been reported.<br>- | Not significant |
| | | See **contraindications** | - Patients should be carefully examined prior to administration to determine signs of acute inflammation, and the physician should evaluate whether Hyalgan treatment should be initiated when objective signs of inflammation are present. | Not significant |
| | | **Dosage and Administration**<br>- If joint effusion is present it should be aspirated before injection of Fermathron | **General**<br>- Remove joint effusion, if present, before injection Hyalgan. | Not significant |

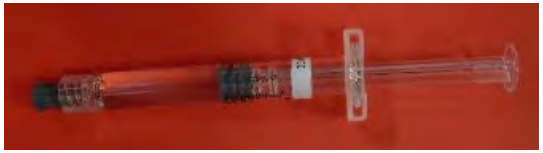
| | | Device under evaluation: | Equivalent model: | Evaluation whether the difference can have a significant clinical impact |
|---|---|---|---|---|
| | | | | |
| | | **Dosage and Administration**<br>- The recommended dosage regimen for patients with mild to moderate osteoarthritis of the knee joint is up to five weekly injections of 2.0 ml into the synovial space of the knee joint.<br><br>**Uses**<br>- Duration of effect in the hip, ankle and shoulder joints has not been demonstrated. | - The effectiveness of a single treatment cycle of less than 3 injection has not been established.<br><br>- The safety and effectiveness of the use of Hyalgan in joints other than the knee have not been established. | Not significant |
| | | **Adverse reactions**<br>- Transient pain and swelling may occur following intra-articular injections.<br>- Rarely an inflammatory reaction, septic arthritis, or arthralgia could occur which may or may not be associated with Fermathron. | **Information for Patients**<br>- Transient pain and/or swelling of the injected joint may occur after intra-articualr injection of Hyalgan<br>- As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities or prolonged (i.e., more than 1 hour) weight- bearing activities such as jogging or tennis within 48 hours following the intra-articular injection. | Not significant |
| | Target patients | Patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint. | Hyalgan is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy, and to simple analgesics, e.g., acetaminophen. | Equivalent target patients |
| | Target users | Injection of Fermathron should only be carried out by a Healthcare Professional trained in the technique. | Physician | Equivalent target users |
| | Mode of application | Fermathron is a clear solution of sterile 1.0% LMW sodium hyaluronate in phosphate buffered saline contained in a pre-filled syringe for single intra- | Hyalgan is supplied as a sterile, non-pyrogenic solution in 2ml vials or 2ml pre-filled syringes.<br>Hyalgan is administered by intra-articular injection. | Equivalent mode of application |

| | | **Device under evaluation:** | **Equivalent model:** | **Evaluation whether the difference can have a significant clinical impact** |
|---|---|---|---|---|
| | | articular injection into the synovial space of the joint. It is recommended that injections in the hip, ankle and shoulder joints are performed using ultrasound or fluoroscopic guidance. | | |
| | Duration of use | The recommended dosage regimen for patients with mild to moderate osteoarthritis of the knee joint is up to five weekly injections of 2.0 ml into the synovial space of the knee joint. The dosage regimen should be adapted by the Healthcare Professional for injection into the synovial space of the hip, ankle and shoulder joints. | A treatment cycle consists of 5 injections given at weekly intervals. (5 weeks)<br>Some patients may experience benefit with 3 injections given at weekly intervals. (3 weeks) | Equivalent duration of use |
| | Number of re-applications | Fermathron is a single use device | The Hyalgan vial/syringe is intended for single use only | Equivalent number of re- applications |
| | Body interaction | Provide support and lubrication to synovial joints. administered by intra-articular injection. | Provide support and lubrication to synovial joints. administered by intra-articular injection. | Equivalent body interaction |
| **Clinical aspects** | Clinical condition (including severity, stage of disease) | Mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint. | For the treatment for pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy, and to simple analgesics, e.g. acetaminophen. | Equivalent clinical condition |
| | Site in the body | Knee, hip ankle and shoulder | knee | Equivalent site in the body, however Fermathron has a wider range of applications in additional synovial joints. |
| | Population | Adults | Adults | Equivalent population |
| **Biological aspects** | Materials in contact with the human tissues or body fluids. | 1.0% linear sodium hyaluronate in phosphate buffered saline | 1.0% linear sodium hyaluronate in phosphate buffered saline | Equivalent biological aspects: devices are of similar composition and are in contact with same human tissues. |

| | | Device under evaluation: | Equivalent model: | Evaluation whether the difference can have a significant clinical impact |
|---|---|---|---|---|
| | Special surface treatment applied | N/A | N/A | N/A |
| | Sodium Hyaluronate source – animal/bacterial | Bacterial | Avian | The HA in Fermathron is not from an avian source, therefore clinical risks associated with this such as allergenic reactions in patients with avian sensitivities, do not apply unlike Hyalgan. HA produced from animal and bacterial sources is equivalent in structure and function as discussed earlier in this report. No significant clinical impact. |
| **Technical Aspects** | Concentration HA | 9.75 – 11.0 mg/ml | 10.0 mg | Not significant. |
| | pH | 6.8-7.6 | 6.8-7.5 | Not significant. |
| | Volume per injection | 2.0 ml | 2.0 ml | No difference. |
| | Chemical composition | Sodium Hyaluronate 9.75 – 11.0 mg/ml<br>Sodium Chloride 7.6 to 9.5 mg/ml<br>Phosphate 0.15 to 0.25 mg/ml<br>Water for injection q.s. | Sodium Hyaluronate 10.0 mg/ml<br>Sodium Chloride 8.5 mg/ml<br>Phosphate 0.65 mg/ml<br>Water for injection q.s. | Same major constituent HA at same concentration. Both in a buffered salt solution. Exact concentration of phosphate in buffer solution differs slightly, however no clinical difference is expected. |
| | Molecular Weight | 1.19 to 2.03 x $10^6$ Daltons | 500,000-700,000 Daltons | No significant clinical impact acticipated as molecular weights are sufficiently similar. |
| | Intrinsic Viscosity | 15.2 to 22.0 dl/g | 8.4-10.6 dl/g (as calculated from stated molecular weight using Mark-Houwink equation) | No significant clinical impact acticipated as intrinsic viscosities are sufficiently similar. |

| | | **Device under evaluation:** | **Equivalent model:** | **Evaluation whether the difference can have a significant clinical impact** |
|---|---|---|---|---|
| | Osmolality | 250 to 335 mOsm/kg | Not stated | No clinical impact expected. Hyalgan has been tested and shown to be biocompatible. |
| | Sterility | Sterile formulation | Sterile formulation | Equivalent |
| | Cannula Size Recommended | 19-20 G | 20 G | Not significant. |

## Table 8b: Comparative table of Fermathron plus and equivalent device, Orthovisc

| | | Device under evaluation | Equivalent model | Evaluation whether the difference can have a significant clinical impact |
|---|---|---|---|---|
| **Device name** | | **Fermathron plus** | **Orthovisc** | N/A |
| **Legal manufacturer** | | **Hyaltech Ltd** | **Anika Therapeutics** | N/A |
| **Relationship to the device** | | Legal manufacturer | Legal manufacturer | N/A |
| **Regulatory status** | | CE marked 05/06/2008 | CE marked<br>PMA P030019 04/02/2004 | N/A |
| **Illustration** | |  |  | Equivalent packaging and route of administration |
| **Intended purpose** | IFU reference | 272-45-K3<br>Revised 01/2015 | AML 500-271/C Revised 08/2012<br>http://orthovisc.cz/wp-content/uploads/2017/04/OV013_Orthovisc_IFU_AML500-271C.pdf | N/A |
| | Indication(s) | For the relief of pain and stiffness of the knee, hip and ankle joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint. | ORTHOVISC is indicated as a viscoelastic supplement or a replacement for synovial fluid in human joints. ORTHOVISC is well suited for treatment of the symptoms of human synovial joint dysfunctions such as osteoarthritis. The actions of ORTHOVISC are lubrication and mechanical support. | Equivalent intended use however Orthovisc has a wider range of applications |

| | | | | |
|---|---|---|---|---|
| | | | In the United States and Canada, ORTHOVISC is approved solely for use in the knee.<br>In the European Economic Area and other parts of the world, ORTHOVISC is approved for use in all synovial joints. | |
| | Contraindication(s) | - Do not inject Fermathron plus if the area of the injection is infected or where there is evidence of skin disease.<br>- Do not use in patients with known hypersensitivity to sodium hyaluronate. | The following pre-existing conditions may constitute relative or absolute contraindications to the use of ORTHOVISC:<br>- known sensitivity to any of the ingredients contained in ORTHOVISC,<br>- pre-existing infections of the skin in the region of the intended injection site,<br>- known infection of the index joint,<br>- known systemic bleeding disorders. | Not significant |
| | | **Precautions**<br>Sodium hyaluronate is manufactured by fermentation of Streptococcus equi and rigorously purified. However, the physician should consider the immunological and other potential risks that can be associated with the injection of any biological material | - ORTHOVISC may contain trace amounts of gram positive bacterial proteins and are contraindicated for patients with a history of such allergies. | Not significant |
| | Precaution(s) | - Do not use after the expiry date.<br>- Do not use if the sterile packaging has been damaged.<br>- Do not use for children.<br>- There is no evidence concerning the safety of Fermathron plus in human pregnancy and lactation. Administration during pregnancy and lactation is at the discretion of the orthopaedic surgeon.<br>- Follow national or local guidelines for the safe use and disposal of needles. Obtain prompt medical attention if injury occurs. | - Those precautions normally considered during injection of substances into joints are recommended. | Not significant |

| | | | | |
|---|---|---|---|---|
| | | - Fermathron plus is a single use device and is intended to be used for a single patient only. If Fermathron plus is used for a second patient the sterility will be compromised and there is a risk of foreign body reaction and/ or infection.<br>- Fermathron plus should not be re-sterilised as the device performance may be compromised.<br>- Fermathron plus should be used with a sterile needle that should be discarded after single use. | | |
| | | **Dosage and Administration**<br>- Injection of Fermathron plus should only be carried out by a Healthcare Professional trained in the technique. | - Only medical professionals trained in accepted injection techniques for delivering agents to intra-articular synovial joint spaces should inject sodium hyaluronate for this application. | Not significant |
| | | - The recommended dosage regimen for patients with mild to moderate osteoarthritis of the knee joint is up to three weekly injections of 2.0 ml into the synovial space of the knee joint. The dosage regimen should be adapted by the Healthcare Professional for injection into the synovial space of the hip and ankle joints. It is recommended that injections in the hip and ankle joints are performed using ultrasound or fluoroscopic guidance. | - An excess amount of sodium hyaluronate is not to be used and the patient should be monitored closely. The space should not be overfilled. If pain increases during the injection procedure, the injection should be stopped and the needle withdrawn.<br>- Patients experiencing abnormal sequelae to the administration of ORTHOVISC or ORTHOVISC mini should consult with a physician immediately. | Not significant |
| | Target patients | For patients requiring the relief of pain and stiffness of the knee, hip and ankle joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint. | Patients requiring treatment of the symptoms of human synovial joint dysfunctions such as osteoarthritis. | Equivalent target patients |
| | Target users | Injection of Fermathron should only be carried out by a Healthcare Professional trained in the technique | Medical professionals trained in accepted injection techniques for delivering agents to intra-articular synovial joint spaces | Equivalent target users |

| | | | | |
|---|---|---|---|---|
| | Mode of application | Fermathron plus is a clear solution of sterile 1.5% HMW sodium hyaluronate in phosphate buffered saline contained in a pre-filled syringe containing 2,0 ml for single intra-articular injection into the synovial space of the joint. | ORTHOVISC is a sterile viscoelastic preparation supplied in a disposable glass syringe containing 2.0 mL (appropriate for larger joints such as the knee) of 1.5% HMW sodium hyaluronate dissolved in physiological saline.<br>Orthovisc is administered by intra-articular injection. | Equivalent mode of application |
| | Duration of use | The recommended dosage regimen for patients with mild to moderate osteoarthritis of the knee joint is up to three weekly injections of 2.0 ml into the synovial space of the knee joint.<br><br>The dosage regimen should be adapted by the Healthcare Professional for injection into the synovial space of the hip and ankle joints. It is recommended that injections in the hip and ankle joints are performed using ultrasound or fluoroscopic guidance. | The recommended treatment regimen is 3 injections spaced one week apart for each treatment course.<br>(3 weeks)<br><br>Not to exceed one treatment course for any individual joint in any 6-month period. | Equivalent duration of use |
| | Number of re-applications | Fermathron plus is a single use device | Orthovisc is a single use device | Equivalent number of re- applications |
| | Body interaction | Fermathron plus is a high molecular weight synovial viscosupplement intended for the relief of pain and stiffness of the knee, hip and ankle joints in patients with mild to moderate osteoarthritis, which is administered by intra-articular injection. | Orthovisc is a high molecular weight synovial viscosupplement or replacement for synovial fluid in human joint dysfunctions, such as in patients with osteoarthritis, which is administered by intra-articular injection. | Equivalent body interaction |
| **Clinical aspects** | Clinical condition (including severity, stage of disease) | For the relief of pain and stiffness of the knee, hip, and ankle joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint. | For treatment of the symptoms of human synovial joint dysfunctions such as osteoarthritis. The actions of ORTHOVISC are lubrication and mechanical support. | Equivalent clinical condition |
| | Site in the body | Knee, hip and ankle | In the United States and Canada, ORTHOVISC is approved solely for use in the **knee.**<br><br>In the European Economic Area and other parts of the world, ORTHOVISC is approved for use in **all synovial joints.** | Equivalent site in the body |

| | | | | |
|---|---|---|---|---|
| | Population | For patients with joint pain resulting from osteoarthritis. | For patients with joint pain resulting from osteoarthritis. | Equivalent population |
| **Biological aspects** | Materials in contact with the human tissues or body fluids. | 1.5% linear sodium hyaluronate in phosphate buffered saline | 1.5% linear sodium hyaluronate in phosphate buffered saline | Equivalent materials in contact with same human tissues. |
| | Special surface treatment applied | N/A | N/A | N/A |
| | Sodium hyaluronate source – animal/bacterial | Bacterial | Bacterial | Equivalent source |
| **Technical aspects** | Concentration HA | 14.0-16.0 mg/ml | 15.0 mg/ml | Not significant. |
| | pH | 6.8-7.6 | Not stated | Not significant. As Orthovisc is made up in physiological saline and has been tested for biocompatibility it can be assumed that the pH is similar to Fermathron plus and that there is no impact on clinical performance or safety. |
| | Volume per injection | 2.0 ml | 2.0 ml | No difference. |
| | Chemical composition | Sodium Hyaluronate 14.0 – 16.0 mg/ml<br>Sodium Chloride 8.5 to 9.5 mg/ml<br>Phosphate 0.15 to 0.25 mg/ml<br>Water for injection q.s. | Sodium Hyaluronate 15.0 mg/ml<br>Sodium Chloride 9.0 mg/ml<br>Water for injection q.s. | Same major constituent HA at same concentration. Both in a buffered salt solution. Exact composition of salt solution differs slightly however no clinical difference is expected. |
| | Molecular Weight | 2.30 to 3.98 x $10^6$ Daltons | 1.0-2.9 x $10^6$ Daltons | No significant clinical impact acticipated as molecular weights are sufficiently similar. |
| | Intrinsic Viscosity | 24.0 – 35.0 dl/g | 13.5-28.1 dl/g (as calculated from stated molecular weight using Mark-Houwink equation) | No significant clinical impact acticipated as intrinsic viscosities are sufficiently similar. |
| | Osmolality | 300 to 360 mOsm/kg | 340 mOsm/kg | No clinical impact expected. |

| | | | | |
|---|---|---|---|---|
| | Sterility | Sterile formulation | Sterile formulation | Equivalent |
| | Cannula Size Recommended | 18-21 G | 18-21 G | No difference. |

### 4.1.3 Clinical, biological and technical characteristics

Equivalent products considered in this review are intra-articular hyaluronic acid viscosupplements and have data to support their use in the same intended use as for Fermathron and Fermathron plus.

All products considered in this review are intended to be used by medical professionals in a clinical environment, and have similar specifications including materials used, molecular weight and concentration.

The characteristics of the equivalent device are sufficiently similar to the device under review to the extent that there will be no clinically significant difference in performance and safety between the equivalent and the target device. The intended uses are also the same with respect to the clinical condition, the severity and stage of the disease, the site of application and the patient population.

Published articles in this review provide data on viscosupplements for the treatment of OA comprising similar hyaluronic acid material, with the same site of implantation in the same population of patients, and therefore the biological parameters are comparable with those of Fermathron and Fermathron plus.

### 4.1.4 Support from pre-clinical studies

See Table 9 below.

### 4.1.5 Conclusions

All products considered in this review are intra-articular hyaluronic acid viscosupplements and have data to support their use in the same intended use as for Fermathron and Fermathron plus.

All products considered in this review are intended to be used by medical professionals in a clinical environment, and have similar specifications including materials used, molecular weight and concentration.

The characteristics of the equivalent device is sufficiently similar to the device under review, Fermathron and Fermathron plus, to the extent that there will be no clinically significant difference in performance and safety between the equivalent and the target device. The intended uses are also the same with respect to the clinical condition, the severity and stage of the disease, the site of application and the patient population.

Through the comparison of the technical, clinical and biological properties, the devices have been demonstrated to be equivalent. Differences are not expected to affect the clinical performance and clinical safety of the device under evaluation.

# 5. CLINICAL DATA AVAILABLE

Details of the literature search and the clinical appraisal of the data selected through the literature search are given in Appendix 1.

## 5.1 Clinical data generated and held by the manufacturer

The clinical data generated and held by the manufacturer is summarised in Table 9 below.

**Table 9: Clinical data generated and held by the manufacturer**

| Name of study / report – Code name if applicable | Version | Date | Status | Device studied | n | Follow-up |
|---|---|---|---|---|---|---|
| **Pre-market clinical investigations*** | | | | | | |
| CT9703 A Phase I double-blind, randomised, controlled comparative study to assess the safety and potential to cause arthus reactions of LMW-SH given by intradermal injections into the arms of healthy volunteers using 0.5% *candida albicans* antigen as a positive control. | NA | 1997 | Completed | Fermathron | 10 | 8, 12, 24 and 48 hrs |
| CT9705 German clinical study of Fermathron<br><br>McDonald C, Hantel S, Strohmeier M. A randomised, controlled study to compare the performance and safety of two sources of sodium hyaluronate given as a viscosupplement by intra-articular injection to patients with osteoarthritis of the knee. J Clin Research. 2000;3:41-50 | NA | 1998 | Completed | Fermathron | 114 | 1,2,3,4,5, 6, 10, 14, 18 weeks |
| **PMCF studies** | | | | | | |
| None | | | | | | |
| **PMS reports** | | | | | | |
| Post Marketing Surveillance Minutes | NA | 07 July 2015 | Revised 29/07/2016 | Fermathron Fermathron plus | NA | NA |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Complaints regarding performance and safety** | | | | | | |
| Extraction from the complaints database (January 2015-January 2018) | NA | 05 Jan 2018 | 5 Resolved 2 Open | Fermathron | 7 | NA |
| | NA | 05 Jan 2018 | 4 Resolved | Fermathron plus | 4 | NA |
| **Details of all fields safety corrective actions** | | | | | | |
| None | | | | | | |
| **Use of a custom made device** | | | | | | |
| Not applicable | | | | | | |
| **Use under compassionate use / humanitarian exemption programs** | | | | | | |
| None | | | | | | |
| **Other** | | | | | | |
| None | | | | | | |

*Note: Two initial clinical investigations were conducted in Sweden (CT9601) and Germany (CT9602) in 1996 to determine the safety and performance of Fermathron, but were terminated following a high incidence of pain and swelling in the treated knees. As a result, the product presentation was re-designed as Fermathron had been supplied in a vial containing 5ml sodium hyaluronate solution, and 5ml had been injected in the trial in Germany, instead of the recommended 2ml, the manufacturing process was also modified to include an additional purification step to overcome any potential immunotoxicity problems. Fermathron was therefore subsequently supplied in a pre-filled sterile syringe filled with 2ml of the viscosupplement. The reformulated product was administered intradermally (0.05ml) to 20 healthy male and female volunteers in a phase I study (CT9703), and results showed that Fermathron was well-tolerated and did not produce any Arthus-type reactions.

### 5.1.1 Fermathron Clinical Investigations

The safety of the Fermathron formulation was established in a phase I study (CT9703), and results showed that Fermathron was well-tolerated and did not produce any Arthus-type reactions.

A phase III, multicentre, randomised, observer blind, controlled, comparative clinical study (CT9705) was set up, which assessed the ability of Fermathron (2ml, 10mg/ml sodium hyaluronate, molecular weight 1.19-2.03x$10^6$ Daltons [previously expressed as 0.8 - 1.3 x $10^6$ Daltons], in phosphate-buffered saline) to reduce pain and stiffness of the knee joint in patients with mild to moderate osteoarthritis (radiologically confirmed Ahlbäck classification I, II or III) of the knee, in comparison with the reference product: Hyalart (2ml, 10mg/ml sodium hyaluronate, molecular weight 0.5 - 0.73 x $10^6$ Daltons of avian origin, in phosphate-buffered saline), manufactured by Fidia Farmaceutici S.p.A., Italy. Hyalart is the German brand name for Hyalgan, which is FDA approved.

The Fermathron study was initiated in 1998 in Germany, and was published in 2000 (McDonald *et al.*, 2000). This study was designed and performed in accordance with European Community Good Clinical Practice (GCP) guidelines (CPMP/ICH/135/95) and the Declaration of Helsinki. Lequesne index scores, which incorporate measurements of pain and discomfort, maximum distance walked and activities of normal living (Lequesne *et al.*, 1987), significantly ($p$<0.0001) decreased from baseline in both treatment groups 3 months after the final injection of a 5 weekly course of intra-articular Fermathron or Hyalart injections, with no statistically significant difference between the groups. Clinically relevant benefits were

demonstrated for a further 3 months as only 9 patients in each group (7.9% of per protocol Fermathron patients and 7.6% of Hyalart patients) required additional therapy to the study knee in this period. The duration of effect was therefore shown to be 6 months. As a secondary outcome, consumption of rescue medication (paracetamol) during the study decreased in both groups, with no statistically significant differences between the two treatments. The safety of the two devices was also comparable. Local adverse events attributed to use of either device (reported in 18.9% of patients who received Fermathron and 13.8% of patients treated with Hyalart) were mostly mild to moderate in severity, with the most common symptom being transient knee joint pain; the majority of patients recovered by the end of the study. No serious adverse events related to the injection of either device were reported. Patient assessment of pain in the treated area on a visual analogue scale, an indicator of both performance and safety, was shown to decrease from baseline over the 3-month study period in both groups of patients. This clinical investigation establishes the comparable safety and performance of Fermathron and Hyalart.

# 5.2 Clinical data from literature

## 5.2.1 Literature search strategy

A summary of the literature search strategy is given in Table 10.

**Table 10: Summary of the literature search strategy**

| | |
|---|---|
| **Objectives** | To identify performance and safety data on Fermathron and Fermathron plus and the equivalent devices Hyalgan (Hyalart) and Orthovisc respectively.<br>Additional brand names Jointlube and Pentavisc (Fermathron) and Kappavisc (Fermathron plus) were also included in the search to maximise relevant results.<br>Materiovigilance public databases including FDA (MAUDE), MHRA were also searched. |
| **Sources** | <PubMed - http://www.ncbi.nlm.nih.gov/pubmed><br><MAUDE - https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm><br>< FDA Medical Device Recalls - https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm><br><MHRA Alerts and recalls for drugs and medical devices - https://www.gov.uk/drug-device-alerts> |
| **Search methodology** | A literature search was carried out to identify, appraise, collate and analyse clinical data for Fermathron and Fermathron plus (including alternative brand names Jointlube, Pentavisc, Kappavisc) and the equivalent devices Hyalgan/Hyalart and Orthovisc respectively, in accordance with MEDDEV 2.7.1 revision 4 Evaluation of Clinical Data. See Appendix 1 for details of the databases searched, keywords used, the selection and appraisal processes, and summary tables of the findings.<br><br>Items resulting from the searches were reviewed for information relevant to the scope of the literature search. If an abstract indicated potential relevant information, the complete article was obtained. Each record or article was reviewed to identify information relevant to the aims of the literature review. Papers cited in articles were also checked for relevant information and were obtained if required.<br><br>A search item was chosen if it focused on Hyaltech IA-HA viscosupplements or on equivalent devices with the same indication for use, similar design, and causing similar medical and technical |

| | |
|---|---|
| | complications as the medical devices under investigation, or if the article indicated something relevant to the state of the art. Only articles with clinical data were selected.<br>An article was excluded if:<br>• It did not fulfil any of the above-mentioned criteria (e.g. news article, training material, book).<br>• The focus of the clinical investigation was on a particular operative technique, rather than the use of IA-HA viscosupplements for the treatment of OA.<br>• The study was performed for an off-label indication.<br>• It reported a case study with very low number of patients (articles were kept in case safety data could be identified).<br>• It involved children<br>• It involved animal studies<br>• If the full paper could not be retrieved<br><br>Searches were conducted to include data from 1st May 2012 to November 2017. |

### 5.2.2 Number of selected outputs

Titles and abstracts from literature search results were initially screened by a single reviewer for relevance and full papers were obtained for potentially relevant citations. If it was not possible to determine eligibility from an abstract, an attempt to obtain the full text article online was made.

A second review of retrieved papers was performed against the eligibility criteria and reasons for the exclusion of papers were documented in the Screening Log (see Appendix 1).

Included papers/studies were then appraised using the 'Appraisal of Pertinent Data' as detailed in clause 9 of MEDDEV 2.7.1 Rev. 4, the results of which are documented in the data extraction table (see section 7).

Methodological quality of studies was assessed with consideration of potential sources of bias related to study design and reporting, in addition to confounding, sample size, setting, source of funding, variability of results, directness of comparisons and applicability. These aspects were also considered in the data analysis of individual studies and evaluation of the dataset as a whole.

Detailed justifications for exclusion are provided in below in the table:

Table - Codes for exclusion (examples)

| Code | Description | |
|---|---|---|
| NE | Non Equivalence | Technical, composition, design...not equivalent device |
| | | Different indication/ claim |
| | | Different population |
| M | Methodology of the described study | Inappropriate number of patients, duration... |
| | | No statistical analysis |
| | | Non comparative study* |
| T | Type of publication | Not a clinical study |
| | | Case reports (CR) |
| | | Poster |
| | | Preclinical study (in vitro/ in vivo) |
| | | Socio-economic assessment, cost-effectiveness study |
| | | Comments on an article |

| Code | Description | |
|---|---|---|
| | | Non peer-reviewed opinion/ journal |
| | | Old/ ancient reference |
| OS | Out of scope | Out of the scope of the review |
| L | Language | Foreign language not generally understood |
| D | Duplicate | Duplicate of article (same author, same study...) |
| *non comparative studies can still give valuable information on performance and safety, plus this may be the only type of clinical data available for some types of device, hence publication may still include- refer to REGTMP-001 | | |

Using PubMed, 40 relevant publications were identified during the literature search. Over the successive up-dates of this clinical evaluation, a total of 40 peer-reviewed papers published between May 2012 and November 2017 have been selected and analysed, as can be seen in Table 11 below:

**Table 11: Summary of the literature retrieval**

| Keywords | | Limits / Filter | Results | |
|---|---|---|---|---|
| | | Pubmed | Total Results | Relevant Results |
| 1 | Fermathron and or Jointlube and or Pentavisc | Human | 1 | 1 |
| 2 | Fermathron plus and or Kappavisc | Human | 1<br><br>1 Exclusion:<br>1 - D | 0 |
| 3 | Hyalart and or Hyalgan | Human | 8<br><br>5 Exclusions:<br>3 - NE | 5 |
| 4 | Orthovisc | Human | 3<br><br>3 Exclusions:<br>2 - NE<br>1 - M/T | 0 |
| 5 | Viscosupplement and/ or viscosupplementation | Human | 145<br>(only the first 30 most relevant results were reviewed)<br><br>16 Exclusions:<br>2 - NE<br>2 - T<br>2 - OS<br>7 - M/T<br>2 - D<br>1 - Full paper could not be retrieved | 14 |

| Keywords | | Limits / Filter | Results | |
|---|---|---|---|---|
| | | Pubmed | Total Results | Relevant Results |
| 6 | Osteoarthritis and hyaluron* (to cover the variations of hyaluronate, hyaluronan, hyaluronic) | Human | 451 (only the first 30 most relevant results were reviewed)<br><br>21 Exclusions:<br>10 - NE<br>3 – M/T<br>1 - M<br>2 - OS<br>1 - M/T<br>4 - D<br>1 - Full paper could not be retrieved | 8 |
| 7 | synovial joint and hyaluron* (to cover the variations of hyaluronate, hyaluronan, hyaluronic) | Human | 112 (only the first 30 most relevant results were reviewed)<br><br>25 Exclusions:<br>4 – NE<br>12- T<br>1 – L (Russian)<br>3 – D<br>1 – Full paper could not be retrieved<br>2 – NE/T<br>1 - M | 5 |
| 8 | Intraarticular and / or intra-articular and hyaluron* (to cover the variations of hyaluronate, hyaluronan, hyaluronic) | Human | 282 (only the first 30 most relevant results were reviewed)<br><br>24 Exclusions:<br>11 – D<br>2 – Full paper could not be retrieved<br>4 – T<br>1 – L (German)<br>6 – NE | 6 |
| 9 | Infection and hyaluron* (to cover the variations of hyaluronate, hyaluronan, hyaluronic) | Human | 271 | 1 |

| Keywords | | Limits / Filter | Results | |
|---|---|---|---|---|
| | | Pubmed | Total Results | Relevant Results |
| | | | (only the first 30 most relevant results were reviewed)<br><br>29 Exclusions:<br>27 – NE<br>1 – T<br>1 – NE/D | |
| **10** | Immunological response and/ or allergy hyaluron* (to cover the variations of hyaluronate, hyaluronan, hyaluronic) | Human | 98<br>(only the first 30 most relevant results were reviewed)<br><br>30 Exclusions:<br>23 – NE<br>2 – T<br>3 – OS<br>1 - NE/OS<br>1 NE/T | 0 |
| **11** | Inflammatory Response and hyaluron* (to cover the variations of hyaluronate, hyaluronan, hyaluronic) | Human | 108<br>(only the first 30 most relevant results were reviewed)<br><br>30 Exclusions:<br>17 – NE<br>10 – NE/T<br>3 – T | 0 |
| Total articles | | | 1480 recovered<br>234 reviewed | 41 |
| Duplicates | | | 21 | N/A |
| Total articles after removal of duplicates | | | 213 | N/A |
| **Total screened articles** | | | 213 | N/A |
| First screening (title/abstract): Total selected articles | | | 40 | N/A |
| Total articles excluded after full-text analysis | | | 0 | N/A |
| **Total analyzed articles** | | | **40** | N/A |

### Surveillance databases

The following national authority databases were searched:

| Search number | Keywords | FDA MAUDE – Adverse Events Results | FDA Medical Device Recalls Results | MHRA (UK) Results |
|---|---|---|---|---|
| **1** | Fermathron | 0 | 0 | 0 |
| **2** | Fermathron Plus | 0 | 0 | 0 |
| **3** | Kappavisc | 0 | 0 | 0 |
| **4** | Hyalart | 2<br>1 death<br>1 injury | 0 | 0 |
| **5** | Hyalgan | 61<br>3 deaths<br>55 injury<br>2 malfunction<br>1 N/A | 0 | 0 |
| **6** | Orthovisc | 117<br>5 deaths<br>76 injury<br>1 malfunction<br>2 N/A<br>33 other | 0 | 0 |
| | **Total** | **180** | **0** | **0** |
| | **Grand Total** | **180** | | |

The MHRA (UK) national vigilance website was also investigated. However, they only provide a means of reporting incidents, serious adverse events and/or field safety corrective actions, i.e. they do not have searchable public databases of adverse events and incidents.

### 5.2.3 Type of selected clinical data

Most studies selected through PubMed (41 papers) were reviews, meta-analyses and prospective, randomised comparative studies. 19 papers were specific to the device under evaluation and the equivalent device, these were included in the appraisal matrix which is summarised below. Other papers relating to general HA usage , background information, state of the art were summarised in the report but not included in the appraisal matrix. PMA studies for equivalent devices, Hyalgan and Orthovisc were added to the appraisel matirx. An overview of the study designs of the selected clinical data is given in Table 12.

**Table 12: Study designs used in the selected literature**

| Study design | Number of studies |
|---|---|
| Meta-analysis | 6 |
| Prospective randomized fellow-eye controlled study | 0 |
| Prospective, randomised, comparative study | 6 |
| Prospective, non-randomised, comparative study | 1 |
| Prospective, non-comparative study | 0 |
| Non randomised parallel cohort investigation | 0 |
| Consecutive cohort report | 0 |
| Retrospective comparative data analysis | 4 |
| Retrospective data analysis | 1 |
| Case report | 0 |
| Review | 2 |
| Unknown | 0 |
| Other | 2 |

| | |
|---|---|
| **Total number of patients recruited in the studies** | 52685 |

| | |
|---|---|
| **Total number of patients treated with the device under evaluation** | 2444 |

The number of patients included in the peer-reviewed RCT studies ranged from 32 to 437 . Overall, the total number of patients included in the 19 papers retained in traceability matrix was 45432, of which 2444 were implanted with the devices under investigation. The follow-up ranged from 0 – 18 months and was adequate to assess the performance and safety of the devices. It should be noted that some of the study patient numbers were undisclosed, particularly in the numerous meta-analyses and reviews which evaluated large numbers of clinical studies and a variety of devices in addition to the device/device predicate being examined. Subsequently this has an effect on the accuracy of the totals listed above.

# 5.3 Summary and appraisal

## 5.3.1 Overview of the literature appraisal

A summary of the literature appraisal is given in Table 13. The overall normalised appraisal score was 7.34, with a minimum of 4.21 and a maximum of 10.0 (Table 3 of Appendix 1 provides derivation of these scores). The highest score relates to the Fermathron versus placebo study in which a randomized, controlled, double-blind trial, 196 patients with symptomatic knee osteoarthritis (mean age ± SD, 59.4 ± 9.9 years, Kellgren-Lawrence grade 1-3) were given either 3 weekly intra-articular injections of HA or saline (placebo). HA was not found to be superior to the placebo at any follow-up (VAS pain 50 m walking from 56.4 to 38.1, $P < .001$, and 58.2 to 39.6, $P < .001$, respectively), however pain and functional scores

(WOMAC scale) improved significantly from baseline up to 6 months. In addition, no serious adverse events were noticed thus reinforcing the safety of the device.

The lowest score came from the Axe et al , 2013, this is review of historic data specific to middle aged athletes, it conclude that IA- HA has a role in the treatment paradigm but is not suitable for the middle aged athlete who is a knee abuser.

### Table 13: Summary of the literature appraisal

| Suitability criteria | | Mean score |
|---|---|---|
| Appropriate device (1 to 3) | | **1.95** |
| Appropriate device application (1 to 3) | | **1.45** |
| Quality assurance (1 to 3) | | **1.45** |
| Appropriate patient group (1 to 3) | | **1.32** |
| Acceptable report / data collection (1 to 3) | | **1.64** |
| Data source type (1 to 3) | | **1.59** |
| Outcome measures (1 to 3) | | **1.36** |
| Follow-up (1 to 3) | | **1.59** |
| Statistical significance (1 to 3) | | **1.23** |
| Clinical significance (1 to 3) | | **1.40** |
| **Total score normalised** (0 lowest quality, 10 highest quality) | **Normalised average** | **7.49** |
| | **Minimum** | **4.21** |
| | **Maximum** | **10.00** |

# 6. Analysis of the clinical data

Hyalgan (Hyalart), the equivalent device to Fermathron, has been available for sale since 1985. Hyalgan (Hyalart) was CE marked in 1987 and later received FDA clearance on 28th May 1997 (PMA P950027). Hyalgan is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy, and to simple analgesics, e.g., acetaminophen.

A double-masked, placebo and naproxen-controlled, multicenter prospective clinical trial with three treatment arms was conducted in the United States as part of the PMA. A total of 495 subjects with moderate to severe pain were randomized into three treatment groups in a ratio of 1:1:1 Hyalgan, placebo or naproxen. Intra-articular injections were administered weekly for a total of 5 injections. Subsequent visits and evaluations took place at weeks 5, 9, 12, 16, 21 and 26. Analysis of a Visual Analogue Scale for pain, a categorical assessment of pain as assessed by a masked evaluator, a categorical assessment of pain as assessed by the subject, as well as safety data and WOMAC analysis were conducted. A total of 333 subjects completed the study with number and time course of discontinuations comparable across treatment groups. All acceptance criteria were met. The total frequencies and reported severities of adverse events were comparable across treatment groups. Severe pain and swelling occurred in 1.2% of Hyalgan treated subjects which met success criteria of <5%.

The PMA also assessed forty non-U.S. clinical trials with Hyalgan, involving a total of approximately 6000 patients for safety only. 26 were controlled and 14 were uncontrolled. In the controlled studies, Hyalgan was compared with either placebo, an active reference treatment (steroids, sulfated mucopolysaccharides, superoxide dismutase) or no treatment. Follow up periods ranged from 2 months to greater than 12 months. Local events such as injection site reaction and injection site pain were the most frequently reported in the controlled non-U.S. trials.

Orthovisc, the equivalent device to Fermathron plus has been available for sale since 1996. Orthovisc was CE marked in 1996 and later received FDA clearance on 4th February 2004 (PMA P030019). ORTHOVISC is indicated as a viscoelastic supplement or a replacement for synovial fluid in human joints. ORTHOVISC is well suited for treatment of the symptoms of human synovial joint dysfunctions such as osteoarthritis. The actions of ORTHOVISC are lubrication and mechanical support. In the United States and Canada, ORTHOVISC is approved solely for use in the knee. However, in the European Economic Area and other parts of the world, ORTHOVISC is approved for use in all synovial joints.

The safety and effectiveness of Orthovisc for the treatment of osteoarthritis of the knee were evaluated in three randomized, controlled, double-blind multicenter studies performed in the U.S. and Canada. Two of the studies (OAK9501 and OAK2001) used unilateral treatment and form the basis of the PMA approval. The other study (OAK9801) used bilateral treatment and was therefore used only for safety assessment. The OAK9501 study included 385 patients at 21 centres and assessed 3 weekly injections of either Orthovisc or saline. The OAK2001 study included 373 patients at 24 centres and assessed three

treatments: 4 Orthovisc injections, 3 Orthovisc injections + 1 arthrocentesis procedure, or 4 arthrocentesis procedures. Follow-up occurred at weeks 7/8, 11/12, 15/16, 21/22 and 27/28.

The PMA conclusions drawn from the studies were that the studies provide evidence of the safety and effectiveness of Orthovisc and that there were no statistically significant differences in the incidence of adverse events in the patients who received Orthovisc compared to those who received each of the control treatments.

In a randomised, controlled, double-blind trial, 196 patients (mean age ± SD, 59.4 ± 9.9 years, Kellgren-Lawrence grade I to III) with symptomatic knee osteoarthritis were given either 3 weekly intra-articular injections of Fermathron plus (n=99) or saline placebo (n=97) (van der Weegen et al., 2015). VAS pain, range of motion, and WOMAC pain, stiffness, and function were measured at 1, 3 and 6 months after final injection. Although pain and functional scores (WOMAC scale) improved significantly from baseline up to 6 months, HA was not superior to placebo at any follow-up (VAS pain 50m walking from 56.4 to 38.1, $p<0.001$, and 58.2 to 39.6, $p<0.001$, respectively). No subgroup analysis resulted in superior outcomes. There were no serious adverse events in either group. Fermathron plus was effective in the management of knee osteoarthritis, and improved knee pain and functional outcome, but was not superior to saline. It should be noted that a recent systematic review and meta-analysis by Altman et al. (2015) challenges the designation of intra-articular saline injection as a "placebo", based on their finding from data in 32 studies involving 1705 patients, that intra-articular saline significantly improved short-term knee pain (SMD = -0.68; 95% CI: -0.78 to -0.57; $p<0.001$; $I2 = 50\%$), whilst long-term knee pain was significantly decreased following intra-articular saline injection in 19 studies involving 1445 patients (SMD = -0.61; 95% CI: -0.76 to -0.45; $p<0.001$; $I2 = 74\%$). This finding raises questions about the extent to which this therapeutic effect is attributable to a true placebo response versus physiologic effects (nociceptive and pathophysiologic benefits) after directly injecting a fluid into the knee joint.

A study by Berenbaum (2012) reviews a randomized controlled trial comparing HMW viscosupplement Go-ON vs LMW Hyalgan in the treatment of symptomatic knee arthritis, with a treatment schedule of 3 weekly injections of IA-HA. The intention-to-treat (ITT) and per-protocol (PP) populations consisted of 217 and 209 patients and 171 and 172 patients in the GO-ON and Hyalgan groups, respectively. ITT WOMAC pain of 47.5±1.0(SE) and 48.8±1.0 mm decreased by 22.9±1.4 mm with GO-ON and 18.4±1.5 mm with Hyalgan after 6 months. The primary analysis was conducted in the PP population followed by the ITT population. Mean (95% CI) differences in WOMAC pain change were 5.2 (0.9 to 9.6)mm and 4.5 (0.5 to 8.5)mm, respectively, favouring GO-ON, satisfying the claim for non-inferiority (lower limit>-9 mm) and for statistical superiority (95% CI all>0, $p=0.021$). A higher proportion of OARSI/OMERACT responders was observed with GO-ON than with Hyalgan (73.3% vs 58.4%, $p=0.001$). Although HMW Go-On outperformed the predicate, LMW Hyalgan, both preparations were well tolerated and showed a reduction in pain with similar safety.

Di Giacomo (2015) investigated the use of Hyaluronic Acid in the treatment of glenohumeral osteoarthritis through prospective follow-up of 61 patients with mild-moderate shoulder OA. 31 patients were treated

with 5 weekly Hyalgan injections plus physiotherapy, whilst the remaining 30 patients received physical therapy only. The group receiving both Hyalgan and physiotherapy showed a significant difference in pain reduction and quality of life with a longer duration of effect.

A prospective randomised trial comparing a single injection of Hyalgan vs Hylan G-F 20 (a cross-linked HA product) in the treatment of knee OA (Khanasuk, 2012) showed that at 26 weeks both patient groups had significantly improved VAS during walking ($p < 0.01$), WOMAC score ($p < 0.01$) and SF-36 ($p < 0.05$) with no statistical differences between groups with a similar safety profile. As the cost of Hylan G-F 20 was much more expensive than that of HA (534 USD vs. 252 USD) Hyalgan provided far better cost-effectiveness with similar performance and safety results. Similarly, a study by Rosen et al. (2016) which examined the cost-effectiveness of IA-HA treatment of knee OA found Hyalgan to be the least cost-effective HA treatment in terms of Cost per Quality Adjusted Life Years (QALY) but still to be more economical than conventional care. It should also be noted that the comparative HA products in this study were of a higher molecular weight and not fully comparable.

Forty patients with medial compartment knee osteoarthritis (OA) were randomly placed into 1 of 2 groups, in a study by Chareancholvanich et al ( 2014). The study group (n = 20) received 2 cycles (at 6-month intervals) of 5 weekly intra-articular hyaluronic acid injections (Hyalgan) after HTO operation. The control group (n = 20) did not receive any intra-articular injections after HTO surgery. Cartilage volume (primary outcome) was assessed by magnetic resonance imaging (MRI) pre-operatively and 1 year post-operatively. Treatment efficacy (secondary outcomes) was evaluated with the Western Ontario and McMaster Universities OA Index (WOMAC) and by the comparison of the total rescue medication (paracetamol/diclofenac) used (weeks 6, 12, 24, 48).

MRI studies showed a significant increase in total cartilage volume of the study group with a loss in the control group. There were significant improvements after surgery in both groups of all WOMAC scores, however no difference was found between the groups.

It was concluded that IA-HA injections may be beneficial for increasing total cartilage volume and preventing loss of lateral tibiofemoral joint cartilage after HTO. Intra-articular hyaluronic acid improved the clinical outcome by reducing NSAID consumption without any severe adverse events, as observed compared to the control group during 1 year of post-operative study.

In addition to the studies described above, a number of systematic reviews and meta-analyses have been published. These are summarised below:

Stitik et al (2017) investigated the effectiveness of three weekly injections compared to five weekly injections of intra-articular sodium hyaluronate on pain relief of knee osteoarthritis or three weekly injections of other hyaluronan products via a systemic review and meta-analysis. Twenty four studies were identified comprising 2168 participants in 30 treated cohorts. Electronic databases, including PubMed and Embase, were searched from January 1980 until November 2015. The study concludes that the findings infer that Hyalgan treatment of knee OA pain with a course of three weekly intra-articular injections may be expected to provide similar relief, comparable to that achieved with a course of five weekly injections of Hyalgan or a course of three weekly injections with other HA products approved for use in the United States. Note that the other HA products are not specified in the paper.

In 2015 Jevsevar et al published a paper in the Journal of Bone Joint Surgery on Viscosupplementation for osteoarthritis of the knee. The study was a systematic review of evidence. Of 628 abstracts identified in the study literature search 545 did not meet the inclusion criteria set by the authors, following full text review a further 64 articles were excluded. This left 19 articles with a total of 4485 patients. The study concluded that this best evidence systematic review, assessing clinical outcomes involving pain relief and functional improvement does not support routine use of Intra-articular HA. The authors found in contrast to previous reviews no significant evidence of publication bias. They state that the patient benefit of intra-articular HA was not clinically important when compared with Intra-articular saline injections used as a placebo. They also concluded that sub dividing by HA preparation molecular weight did not change the results of the analysis.

A systemic review by Campbell et al, in 2015 looked at the question- Is Local Viscosupplementation Injection Clinically Superior to Other Therapies in the Treatment of Osteoarthritis of the Knee? The review was of overlapping meta analyses. A total of 105 abstracts were reviewed for inclusion in the analysis, with 18 abstracts meeting the authors eligibility criteria for full text review, a further 4 were then excluded leaving a total of 14 studies to be included in the systemic review. Of the 10 studies that examined the effects of Intra- articular Hyaluronic acid (IA-HA) versus Intra- articular placebo, 5 found that IA-HA resulted in pain and 4 found improvements in function, however 3 found no difference between IA-HA and IA-placebo in terms of pain and 4 found no difference in function. The remaining studies showed no clinically relevant differences in pain or function. 3 studies examined IA-HA vs oral NSAID's. No clinically relevant differences in efficacy were found. IA-HA was found to have a slightly improved adverse reaction provided that NSAID's due to the risk of gastrointestinal side effect posed by NSAID's. Both IA-HA and IA- PRP led to improvements in knee function at both 2 and 6 months after injection, positive effects of IA-HA were less robust that those of IA- PRP. IA-HA versus IA-corticosteroids showed better pain relief during the first 4 weeks with IA- corticosteroids but the positive effects of IA-HA were greatest at 5- 13 weeks post injection, this relief persisted up to 26 weeks in two of the studies reviewed by the authors. According to this systematic review of overlapping meta-analyses comparing IA-HA with other nonoperative treatment modalities for knee OA, the current highest level of evidence suggests that IA-HA is a viable option for patients with knee OA. Its use results in improvements in knee pain and function that can persist for up

to 26 weeks in comparison with other treatment modalities. IA-HA has been shown to have a good safety profile, and its use should be considered in patients with early knee OA.

Henrotin et al published a consensus statement on viscosupplementation with hyaluronic acid for the management of osteoarthritis in 2015. Eight European experts were selected according to their expertise in osteoarthritis and viscosupplementation. Five of the eight were rheumatologists, 2 orthopaedic surgeons and one physiotherapist. The experts discussed 24 statements on HA and VS. Agreement was achieved on some recommendations. In particular, the experts achieved unanimous agreement in favor of the following statements:

VS is an effective treatment for mild to moderate knee OA;

VS is not an alternative to surgery in advanced hip OA;

VS is a well-tolerated treatment of knee and other joints OA;

VS should not be used only in patients who have failed to respond adequately to analgesics and NSAIDs; VS is a "positive" indication but not a "lack of anything better" indication; the dosing regimen must be supported by evidence-based medicine; cross-linking is a proven means for prolonging IA residence time of HA; the best approach to inject accurately knee joint is the lateral mid-patellar one; when VS is performed under fluoroscopy, the amount of radiopaque contrast agent must be as low as possible to avoid viscosupplement dilution.

These clear recommendations have been established to help practitioners in the use of viscosupplementation.

Trojian et al (2016) conducted a similar review of data from 1960 to August 2014, from that review 11 papers were included in the systemic review by the authors. The average age of the participants in the studies included in this analysis was over 60 years. In most studies, the participants' severity was Kellgren-Lawrence grade 2 or 3. The average body mass index of the participants in all studies was categorised as overweight or obese. Most studies followed the participants for a total duration of 6 months or the equivalent 26 weeks, with one at 12 weeks and one at 18 weeks. The number of injections varied from a single dose to 5 weekly injections depending on the preparation. The sample size of all but one study was more than 200 with a maximum of 588 participants with a mean of 336 participants. Their position statement on the treatment of knee OA with viscosupplementation injection versus placebo and steroid is based on the evaluation of treatment effect by examining the number of participants within a treatment arm who met the Outcome Measures in Rheumatoid Arthritis Clinical Trials- Osteoarthritis Research Society International (OMERACT-OARSI) criteria which is different and more relevant than methods used in other reviews which examined if the average change across the treatment groups was clinically different. The authors believe it is important to look at the potential of an individual to improve due to a treatment given by injection when compared to the potential for improvement due to a treatment given by another therapeutic or placebo injection. They performed a network meta-analysis (NMA) of the relevant literature to determine if there is a benefit from high molecular weight and/or low-molecular weight HA as compared to intra-articular corticosteroids (IAS) and intra-articular placebo (IAP). To do so, they compared the percentage of individuals with knee OA who achieved improvement as defined by the OMERACT-OARSI responder criteria among those treated with HA, IAS or placebo injection. Results demonstrate

evidence of a small but statistically significant improvement for the group of participants treated with HA injections compared to those treated with IAS or IAP injections with regard to pain and function as assessed by the relevant WOMAC subscales. Furthermore, on an individual level, results indicate that HA instillation led to a 15% and 11% greater chance of achieving OARSI responder status than did IAS and IAP, respectively. This was considered to be statistically significant.

Legré-Boyer (2015) conducted a review aiming to determine good practice and indications for viscosupplementation as a local treatment for symptomatic OA, so as to optimise efficacy. The study states that viscosupplementation has demonstrated moderate but significant efficacy (20%) versus placebo in terms of pain and function, with a high rate of responders (60-70%) in knee osteoarthritis. It allows reduced administration of opioid analgesics and NSAIDs, with improved risk/benefit ratio, and may delay joint replacement. Cartilage protection remains to be proven. Clinical efficacy shows 1-4 weeks' later onset than corticosteroids, but is maintained for 6 or even 12 months. Systematic association of corticosteroid and HA injection is not justified, and an interval has to be left before undertaking arthroplasty. Intra-articular injection of HA requires a skilled specialist, and may be difficult in a non-swollen joint. In other joints than the knee, radiologic or ultrasound guidance is recommended. The efficacy of viscosupplementation is a matter of ongoing debate, after discordant findings in some meta-analyses. Some poor results may be due to inappropriate use of HA injections, poorly adapted to the patient's OA phenotype. The ideal indication in the knee seems to be moderate femorotibial OA without swelling. Results have been generally disappointing in hip osteoarthritis but promising in OA of the ankle and shoulder (with and without rotator cuff tear). The author concludes that further studies are needed to determine response profile and optimal treatment schedule, according to the joint.

Migliore et al (2015) looked at the discrepancy between recommendations and clinical practice for viscosupplementation in osteoarthritis. They stated that recently the American Association of Orthopedic Surgeons (AAOS) and the American College of Rheumatology (ACR) revised their recommendations for the management of knee OA and for hand, knee and hip respectively. AAOS recommendations regarding the management of knee OA report with a recommendation whose strength was defined as “strong” that they cannot recommend the use of intra-articular hyaluronic acid. This recommendation was obtained after the examination of 14 studies (three high-strength studies and 11 moderate-strength studies) and was based on the lack of evidence of efficacy and not on potential harm induced by such kind of treatment. ISIAT Technical Expert Panel (TEP) gathered the following eight suggestions regarding the drawing of recommendations on the use of IAHA in OA and its comparison with other treatments. It is necessary to merge data coming from both RCTs and registers. Only studies with a strong level of evidence should be taken into account. A common threshold of efficacy should be assessed for comparing treatments. Evaluation of hard outcomes is essential. The effect size of placebo as comparator should be attentively considered in RCTs. Particular attention should be given to different phenotypes of OA that may possibly respond differently to each treatment. Compliance and long-term side effects of different therapeutic approaches should be evaluated. Pharmacoeconomic evaluation should be performed on the long term. The conclusions of the review are related more to recommendation for data capture rather than clinical outcomes. Bannuru RR, Vaysbrot, McIntyre looked at the same subject in 2014, highlighting that in the authors opinion the AAOS recommendation was flawed as they looked purely at minimally

clinical important information (MCII) rather than in combination with treatment effect. They concluded that MCII should be used as a supplementary instrument rather than a basis for clinical decision and should not lead to dismissal of clinically viable treatment options.

An investigation by Zychowicz et al. (2014) examines the safety and efficacy of a number of IA-HA products including Hyalgan and Orthovisc.

In 3 double-blind, randomized controlled trials comparing Orthovisc with placebo, HA+arthroscopy and arthroscopy alone significant improvement in pain on walking was seen in the first trial, with non-significant improvements in WOMAC pain scores for the latter two trials. The IA-HA treatments were well tolerated with no significant differences between control groups, demonstrating an acceptable safety profile.

In 6 double blind and 2 single blind RCTs comparing Hyalgan with a number of different alternative treatments including placebo, naproxen, differing numbers of HA injections and arthroscopy, Hyalgan was found to be superior to the alternative treatment in 7 out of 8 trials. Similarly incidence and severity of AEs were found to be comparable between Hyalgan and control groups in 2 of the trials, 4 trials reported minor or no safety events and 2 trials found a greater occurrence of HA related events overall in comparison to the control groups.

A paper by Ray (2013) examines and summarises a number of studies of both Hyalgan and Orthovisc versus placebos, amongst other viscosupplements, in the treatment of knee OA. Hyalgan vs placebo showed significantly greater efficacy in 9 out of 13 studies, however 2 of these studies showed the equivalence of Hyalgan to placebo at other follow-up points or for overall effect in the study. Orthovisc showed similarly promising results and showed greater efficacy than placebo in 4 out of 5 studies, although 2 of which showed equivalence to placebo for global assessment scores and WOMAC pain scores. Efficacy studies within the same review comparing Orthovisc and Hylan G-F 20 showed that Hylan G-F 20 was not superior to Orthovisc for HSS pain score or using the WOMAC pain scale. Overall the review showed that IA-HAs including Hyalgan and Orthovisc are safe and effective in the treatment of symptomatic OA with few adverse events or systemic side-effects.

Trigkilidas and Anand looked at the effectiveness of hyaluronic acid intra- articular injections on managing osteoarthritic knee pain in 2013. They conducted a systemic review of the literature which was performed using MEDLINE®, Embase™ and CINAHL® (Cumulative Index to Nursing and Allied Health Literature). The databases were searched for randomised controlled trials available on the effectiveness of HA intra-articular injections in managing osteoarthritic knee pain. The search yielded 188 studies. Of these, 14 met the eligibility criteria and were reviewed in chronological order. Of the 14 studies, 12 compared HA with a placebo, 5 of these studies showed no statistically significant difference between the two groups. Of the remaining 7 studies one suggested an effect in favour of HA for up to a year following injection, another for up to six months following injection. Three studies suggested a statistically significant superiority of HA over placebo bot only for a short time not exceeding 18 weeks. The final two studies showed a modest effect in favour of HA over placebo for pain that was noticeable at six months but not

for function. Of the two studies that compared HA with steroid injection, one showed no statistically significant difference between the two groups, the other suggested that HA was better at six months than steroid injections but the study has a high drop out rate at 6 months making the results questionable. The authors conclude that overall, there appears to be a small effect with the use of HA over placebo, which peaks around week 8 following the last injection. There is very little evidence to support that the effect is still noticeable at six months. Compared with steroids, steroid injections tend to be superior to HA up to four weeks, with HA becoming superior after that timeframe.

In 2013 Migliore et all published on the safety of intra- articular hip injection of hyaluronic acid products by ultrasound guidance. The authors established a standardised technique for ultrasound guided intra-articular injection of the hip joint with the purpose of extending routine intra-articular injection of hyaluronans and steroids to the hip, as commonly used in the knee. The study was a restrospective multicentre study, looking at patients who attended between 2005 and 2008 with mono or bilateral symptomatic hip OA according to ARA criteria, refractory to therapy with radiological OA graded II-IV (Kellegren and Lawrence ) assessed with the two preceding months. 1906 patients received 4002 injections, the products used were as follows, Hyalgan, Hyalubrix, Jointex, Synvisc, Ortoial, euflexxa. Synvis was the most widely used product, Euflexxa the least. The authors concluded that the treatment was well tolerated with few, and exclusively local, side effects. They believe that, even if fluoroscopy or CT guidance can, on occasion, be justified, nevertheless for general and repetitive use physicians should use the ultrasound technique that eliminates use of radiation and is cost-saving. The technique has proved well tolerated, despite the advanced age of the patients and the high clinical and radiological degree of disease in some cases.

**Summary: Overall, the studies confirm that Hyalgan and Orthovisc, and therefore Fermathron and Fermathron plus, are safe and effective in achieving their intended use and are comparable in performance to other intra-articular hyaluronic viscosupplements currently available on the market. In a recent randomised, controlled, double-blind trial Van der Weegen concluded that Fermathron plus was effective in the management of knee osteoarthritis, and improved knee pain and functional outcome. No serious adverse events occurred.**

# 6.1 Comprehensive analysis of the safety data / Requirements on safety

Injection technique is of prime importance for both efficacy and tolerance in all joints. It is critical that the injection is strictly intra-articular and that aseptic techniques are followed. The following recommendations were made in the 2015 review by Legre-Boyer:

| | Knee | Hip | Shoulder | Ankle |
|---|---|---|---|---|
| **Approach** | Lateral lateropatellar | Anterior or anterolateral | Anterior (radioscopy) or posterior (US) | Anteromedial or anterior |
| **Guidance** | No (except difficult cases) | Radioscopy or US | Radioscopy or US | No or radioscopy > US |
| **Quantity per injection** | 2-6 ml | 2-4 ml | 2-4 ml | 2-3 ml |

A study by Cheng and Abdi entitled Complications of Joint, Tendon and Muscle injections published in 2007 looked specifically at complications in relation to each joint, the relevant sections of the paper are summarised below.

### 6.1.1 Hip injections

As accessing the hip joint is more challenging than the knee ultrasound or radioscopic guidance is recommended. Mild pain or swelling at the site of injection may occur in a small percentage of patients, although severe local inflammation, warmth, and joint effusion are rare (Legre-Boyer 2015).

Air embolism has been reported in pediatric patients during hip joint arthrography. As an aid to correctly placing the needle tip within the hip joint during arthrography, injection of small amounts of air has been used to outline the joint space. The authors noted, over a period of seven years, air embolus in three pediatric patients, twice with minor symptoms, and once with cardiac arrest. They concluded that even small amounts of air (less than 5 cc) injected accidentally intravenously may cause dangerous complications in small infants. Fortunately, this complication has not been reported in adult population. If this technique is to be used, it is recommended that small amounts of carbon dioxide or oxygen be used instead of air.

Further, steroid injection of the greater trochanteric bursa is commonly conducted for bursitis and hip pain. It is generally a safe procedure, but not without complications.

### 6.1.2 Knee injections

Intra-articular viscosupplementation with hyaluronate-derived products has gained popularity as a palliative modality for the treatment of osteoarthritis of the knee. Knee joint steroid injection is also commonly performed for pain management of osteoarthritis. Although several techniques have been described, it is usually performed by either medial or lateral approach with the flexed affected knee. Complications of knee injections have been related to pain or swelling at the site of injection, granulomatous inflammation of the synovium, saphenous neuropathy, aseptic acute arthritis, septic arthritis, embolia cutis medicamentosa (Nicolau Syndrome), and albicans arthritis.

Mild pain or swelling at the site of injection may occur in up to 20% of patients, although severe local inflammation, warmth, and joint effusion are rare (acceptance criteria of <5% were set during the PMA study for Hyalgan in the United States, actual value obtained was 1.2%). Legre-Boyer (2015) report frequency of pain/inflammation at 2-6% in the knee.

Iizuka et al. (2005) presented a case of obese patient who developed saphenous neuropathy following knee joint injection via medial approach. The clinical picture suggests that the needle pierced the nerve during the procedure. This complication should be considered when performing knee joint injection, especially when the patient is obese and the anatomic landmarks are obscured. Aseptic acute arthritis can develop within hours after injection. Based on standard crystal analysis, calcium crystal shedding has been postulated to explain this complication. However, it is not known whether apatite crystals or low amounts of calcium pyrophosphate dihydrate (CPPD) crystals are also involved as to determine this requires a complete synovial fluid (SF) analysis Further studies are required to investigate possible direct proinflammatory effects of hyaluronic acid degradation products.

Roos et al. (2004) reported a case of acute arthritis after intraarticular injection of sodium hyaluronan (Ostenil) in a 70-year-old woman with a history of knee osteoarthritis. The joint fluid was purulent, with no crystals, and laboratory tests showed marked inflammation, leading to antibiotic treatment for suspected septic arthritis. Incapacitating symptoms persisted, prompting surgical lavage of the knee, which failed to relieve the severe pain. The persistent symptoms and negative results of joint fluid and blood cultures led to discontinuation of the antibiotic therapy after 10 days. Anti-inflammatory therapy relieved the symptoms, and the patient was discharged home 1 month after her admission. Nevertheless, the pain persisted, requiring rehabilitation therapy of the knee. It is suspected that aseptic arthritis induced by repeated sodium hyaluronan injection is the most likely diagnosis. Further, septic arthritis has been reported after intra-articular steroid injection (Charalambous et al. 2003) In a survey of 100 orthopedic surgeons, 100 rheumatologists, and 50 general practitioners in the United Kingdom, 24 respondents (12.6%) had encountered septic arthritis after steroid injection of the knee (18 once, 3 twice, 2 three times, 1 several times). There is a wide variation in the precautions taken to avoid such a complication, 57.6% of the respondents used alcohol swabs to clean the skin, and the remaining 42.4% used chlorhexidine or Betadine. Only 16.3% used sterile towels to isolate the injection site. There were 32.5% of respondents who routinely used sterile gloves when injecting and a total of 46.6% used either sterile or non-sterile gloves. Also, 91.1% changed needles between drawing the steroid and injecting it into the joint. It is not clear whether the minimal use of antiseptic techniques is responsible for the septic arthritis reported.

Lequerre et al. (2002) reported a case of actinomyces naeslundii septic arthritis developed after intra-articular injection of hyaluronate in a man with osteoarthritis of the knee. Actinomyces is an anaerobic Gram-positive rod. The patient was treated successfully with two antibiotics and arthroscopy. The nature of the organism and its location to a joint are unusual features of this case, which illustrates the need to search for a septic complication before accepting a diagnosis of inflammation related to hyaluronate injection.

Evanich et al. (2001) reported one case of septic arthritis among 80 knees with symptomatic osteoarthritis treated with hyaluronic acid. The authors recommend intraarticular hyaluronic acid only for symptomatic patients with significant surgical risk factors and for patients with mild radiographic disease who have failed to respond to conservative treatment such as physical therapy, weight loss, nonsteroidal anti-inflammatory medication, and intraarticular steroid injection. It is inadvisable to treat patients with a complete collapse of joint space or bone loss with intraarticular hyaluronic acid, given their poor clinical response.

Beissert et al. (1999) described a case of embolia cutis medicamentosa after intra-articular injections into the knee. Embolia cutis medicamentosa (Nicolau Syndrome) is a very rare complication of intramuscular injections which presents with extensive necrosis of the injected skin area. Intra-arterial and/or para-arterial injections after prior perforation of certain vessels are considered as possible pathogenetic mechanisms.

### 6.1.3 Shoulder injections

Shoulder injections include subacromial steroid injection and intraarticular injections. Although uncommon, infection is a significant complication of such injections. Strict adherence to aseptic technique is emphasized for performing subacromial corticosteroid injection.

A study by Porcellini et al. (2015) examined the efficacy of intra-articular injections of Hymovis (Fidia Farmaceutici) in patients with glenohumeral joint OA in 41 patients. Overall the treatment was well tolerated. Nineteen AEs were reported during the study in 14 patients but none of them was considered related to the study product. The most common AEs were flu (mild or moderate and reported by six patients) and mild headache (experienced by 3 patients). During the course of the study just two serious AEs occurred, neither of which was related to HYADD®4-G.

### 6.1.4 Ankle injections

Ankle osteoarthritis (OA) is chronic and debilitating condition which is common due to the weight-bearing properties of the joint. Primary osteoarthritis of the ankle is rare, most commonly secondary to fracture or ligament chronic instability. There are few published studies on the use of HA in the literature. A systematic review of viscosupplementation in ankle osteoarthritis conducted by Faleiro et al. in 2016 concluded that treatment with intra-articular hyaluronic acid is a safe therapeutic modality, which promotes a significant improvement of patients' functional scores, with no evidence of superiority over other conservative treatment measures.

No systemic adverse events were reported in the literature relating to ankle viscosupplementation. In the study by Salk et al. (2006), injection site pain was noted in 5 (29%) of the 17 patients including 3 in HA group and 2 in the saline solution group, with no significant difference between the groups. This injection site pain typically lasted no more than 3 days. In a study by Sun et al. (2006) local adverse events occurred in 6.7% of patients during five weekly intra-articular viscosupplementation treatments. Overall the injections were well tolerated with 5 patients experiencing transient pain and erythema at the injection site which resolved within 48 hours and did not affect subsequent injections.

### 6.1.5 Safety data from national authority surveillance databases

Searches were conducted using MAUDE (Manufacturer and User Facility Device Experience database, which is the FDA's database for voluntary reporting of medical device adverse events. Searches were also performed in the FDA Medical Device Recall Database and the MHRA (UK) national vigilance website. It

should be noted however, that the MHRA database only provides a means of reporting incidents, serious adverse events and/or field safety corrective actions, i.e. they do not have searchable public databases of adverse events and incidents.

### Surveillance databases

The following national authority databases were searched from the 1st May 2012 to the present:

| Search number | Keywords | FDA MAUDE – Adverse Events<br><br>Results | FDA Medical Device Recalls<br><br>Results | MHRA (UK)<br><br>Results |
|---|---|---|---|---|
| **1** | Fermathron | 0 | 0 | 0 |
| **2** | Fermathron Plus | 0 | 0 | 0 |
| **3** | Kappavisc | 0 | 0 | 0 |
| **4** | Hyalart | 2<br>1 death<br>1 injury | 0 | 0 |
| **5** | Hyalgan | 61<br>3 deaths<br>55 injury<br>2 malfunction<br>1 N/A | 0 | 0 |
| **6** | Orthovisc | 117<br>5 deaths<br>76 injury<br>1 malfunction<br>2 N/A<br>33 other | 0 | 0 |
| | **Total** | **180** | **0** | **0** |
| | **Grand Total** | **180** | | |

As expected, there were no returns of adverse event reports for Fermathron, Fermathron plus or Kappavisc in the MAUDE searches, as the products are not approved or available in the U.S.

The table summarises the event types listed in FDA MAUDE:

| Event type | Hyalart | Hyalgan | Orthovisc |
|---|---|---|---|
| Septic Arthritis | 1 | | |
| Swelling | 1 | | 8 |
| Allergy/ possible allergy | | 10 | 43 |
| Death ( not device related) | | 1 | |
| Gout | | 1 | |
| Swelling ( hand) | | 1 | |
| Infection/ possible infection | | 17 | 7 |
| Joint pain and swelling | | 14 | 7 |
| Not device related | | 11 | 10 |
| Off Label Use | | 5 | 1 |

| | | | |
|---|---|---|---|
| Patient medical condition | | 1 | 3 |
| Unknown | | 2 | 11 |
| Death (Unknown cause) | | | 2 |
| Death ( allergy) | | | 2 |
| Constipation | | | 1 |
| Diarrhea | | | 1 |
| Arrhythmia/ stroke | | | 1 |
| Immune response | | | 2 |
| Joint pain | | | 7 |
| Mania and allergy | | | 1 |
| Pain | | | 2 |
| User error/ possible user error | | | 4 |
| Product didn't work | | | 1 |
| Syringe Damage | | | 1 |

The most significant numbers of events for both Hyalgan and Orthovisc were allergy/ possible allergy, infection/ possible infection, joint pain and swelling. The information available did not state whether the incidents were device related or not in the majority of cases. Where not device related was stated it is included in the table above. Orthovisc events were as a rule based on individual reports from patients, as such the information available was very much from a lay perspective and not generally clear on how the incident related or did not relate to the device. In summary, events where there were significant numbers were all known and anticipated events for viscosupplementation therapy. It is not possible to further investigate causes of the various single events of a random type. Hyaltech has never had reports or feedback suggestive that any of the more unusual events listed above could occur with Fermathron and Fermathron Plus. No new risks or side effects presented with any of the viscosupplements listed in the table above . The unedited searches including the full reports are attached. None of the events were found to undermine the established safety of the products.

### 6.1.6 Summary of post-marketing surveillance results for Fermathron and Fermathron plus

Customer complaints are managed according to procedure QOP Q158 and logged and managed through a database. A review of all complaints for Fermathron and Fermathron plus in the last three years (since January 2015) is shown in Table 14 below.

**Table 14: Fermathron and Fermathron plus complaints history**

| Reference | Subject | Defect |
|---|---|---|
| 1032605 | Fermathron | Missing variable data |
| 1046928 | Fermathron | Bubbles in syringe |
| 1056184 | Fermathron | Missing variable data |
| 1078887 | Fermathron | Inflammation (28 patients) |

| | | |
|---|---|---|
| 1078894 | Fermathron | Inflammation (24 patients) |
| 1094003 | Fermathron | Missing variable data |
| 1094004 | Fermathron | Wrong Tyvek |
| 1048627 | Fermathron plus | No defect – difference in how concentration is displayed on artwork components. |
| 1074906 | Fermathron plus | Inflammation (3 patients) |
| 1079668 | Fermathron plus | Inflammation (34 patients) |
| 1093686 | Fermathron plus | Inflammation (1 patient) |

Fermathron and Fermathron plus complaint rates for Inflammation in FY/2016/2017 were 0.017% and 0.025% respectively, with the majority reported from Russia. Inflammation is a known risk associated with viscosupplementation using HA and incidence is well within typical rates reported for similar products in the literature.

One Fermathron plus complaint was reported by a customer to the Regional Office of Federal Service for Supervision of Healthcare in the Republic of Mordovia, Russia. On investigation no corrective action was required and the incident was therefore deemed non-reportable in other regions.

The absence of reportable adverse events received for Fermathron and Fermathron plus is evidence of the continued safety of the devices in clinical practice.

Overall the complaints ratio is at a very low level in relation to number of units sold. No new risks have been identified.

### 6.1.7 Requirements on safety

Risks and safety concerns are summarised in Table 15.

All information supplied by the manufacturer has been reviewed and is consistent with the clinical data presented previously.

**Table 15: Summary of the risks and safety concerns**

| Reference | | Safety requirements | Summary of findings from safety analysis |
|---|---|---|---|
| **Identification of the information materials supplied by the manufacturer** | | | |
| **IFU** | Fermathron Sodium hyaluronate 20mg/2.0 ml | **Contraindications:** Do not use in patients with known hypersensitivity to sodium hyaluronate. | There is no evidence concerning the safety of Fermathron in human pregnancy and lactation. Administration during pregnancy and lactation is at the |

| | | | |
|---|---|---|---|
| | Revised 01/2015<br><br>Fermathron plus IFU<br>Sodium Hyaluronate 30mg/2.0ml<br>Revised 01/2015 | | discretion of the orthopaedic surgeon.<br><br>The contra-indications are consistent with the current state of knowledge of the device. |
| | | **Adverse reactions**<br>Transient pain and swelling may occur following intra-articular injections.<br>Rarely an inflammatory reaction, septic arthritis, or arthralgia could occur which may or may not be associated with Fermathron.. | The adverse reactions are consistent with the current state of knowledge of the device. |
| | | **Warnings:**<br>Do not use if the sterile packaging has been damaged.<br><br>Fermathron/Fermathron plus is a single use device and is intended to be used for a single patient only. If Fermathron is used for a second patient the sterility will be compromised and there is a risk of foreign body reaction and/or infection. Fermathron/Fermathron plus should not be re-sterilised as the device performance may be compromised.<br>Fermathron should be used with a sterile needle that should be discarded after single use.<br><br>Fermathron/Fermathron plus has not been tested for compatibility with other substances for intra-articular injection. Therefore the mixing or simultaneous administration with other intra-articular injectables is not recommended.<br><br>Sodium hyaluronate is manufactured by fermentation of Streptococcus equi and rigorously purified. However the physician should consider the immunological and other potential risks that can be associated with the injection of any biological material.<br><br>Do not inject Fermathron /Fermathron plus if the area of the injection is infected or where there is evidence of skin disease.<br><br>Do not use after expiry date.<br><br>Do not use for children.<br><br>Follow national or local guidelines for the safe use and disposal of needles. Obtain prompt medical attention if injury occurs. | The warnings are typical for single use devices delivered sterile.<br><br>Precautions for use are clearly stated in the leaflet.<br><br>They are consistent with the current state of knowledge of the device. |
| | | **Training requirements:**<br>Injection of Fermathron/Fermathron plus should only be carried out by a Healthcare Professional trained in the technique | Training requirements for use are clearly stated in the leaflet. |
| **Labelling** | Not applicable | No requirements on safety besides appropriate harmonised symbols are specified on the labelling. | N/A |

| | | | |
|---|---|---|---|
| **Promotional materials** | Not applicable | **Safety information provided:** No requirements on safety are specified on the promotional materials. | N/A |
| **Inputs from risk management** | | | |
| Risk Management Report for Fermathron/Fermathron plus (V001) | | Product used after blister seal damaged so syringe & possibly viscosupplement no longer sterile | Adequately covered by instructions for use and use of symbol on packaging. |
| | | Product used after storage outside required conditions causing product to degrade. | |
| | | Use after product expiry date -product characteristics degrade or are no longer sterile. | |
| | | Use with other substances for intra-articular injection despite compatibility being unknown | Adequately covered by instructions for use. |
| | | User removes syringe from blister tray but injection procedure is delayed. Previously sterilised outer surface of syringe could come into contact with bioburden prior to use in patient. | |
| | | Infection at injection site prior to injection or injection site/needle used not clean and bacteria introduced | Adequately covered by instructions for use |
| | | Intra-articular injection results in pain and swelling at the injection site | |
| | | Joint effusion, if present, is not aspirated prior to injection of product. Insufficient space within joint to allow full administration of dose. | |
| | | Product contains sodium hyaluronate which could induce a hypersensitivity reaction. Immunological and pyrogenic response | |
| | | Inappropriate use:Too many injections given or user administers too much solution from that supplied | Adequately covered by instructions for use |
| | | Too few injections given or user administers insufficient solution from that supplied | |
| | | Product is injected into surrounding tissues rather than synovial joint. | |
| | | Healthcare professional uses needle which is not compatible with syringe or viscosity of product (e.g. inappropriate gauge) which causes needle detachment or difficulty of injection. | |
| | | Inappropriate use: Product is used for patients with severe arthritis | |
| | | Inappropriate use: Product is used for patients without arthritis, possibly presenting with symptoms of another condition | |
| | | Inappropriate use: Product is used in joints other than knee, hip, shoulder or ankle (off-label use) | |
| | | Multi-use of syringe or needle leading to cross-contamination | Adequately covered by instructions for use and use of symbol on packaging. |
| | | Re-sterilisation of syringe | Adequately covered by instructions for use and use of symbol on packaging. |
| | | Incorrect syringe or needle disposal | Adequately covered by instructions for use |
| | | Use in pregnant or lactating women despite compatibility being unknown | Adequately covered by instructions for use |

| | | |
|---|---|---|
| | Product is used by a person who is not a healthcare professional and/not trained in the procedure of intra-articular injection. | |
| | Use in children despite effect on children's growing joints being unknown | |
| **Analysis of special design features posing safety concerns** | | |
| Not applicable. There are no special design features, including medicinal or animal components posing safety concerns. | | |

### 6.1.8 Conclusion on safety

Patient numbers and follow-up were adequate to determine if the devices were acting as intended and to observe the emergence of adverse events and complications. Taken as a whole, the body of data for Fermathron/Fermathron plus and predicates Hyalgan/Orthovisc is of sufficient quality and relevance to enable conclusions to be drawn about the performance and safety of the devices.

Overall, sufficient evidence was available to support and demonstrate every safety claim. The safety of the device was demonstrated and in compliance with the MDD ER1. The demonstrated claims are summarised in Section 2.7.

## 6.2 Comprehensive analysis of the performance data / Requirements on performance

There are many varieties of performance measurements in the treatment of joint osteoarthritis, however the main methods can be seen below:

| Performance Measurement and description | Description | Scale/Subscale |
|---|---|---|
| Western Ontario McMasters Arthritis University (WOMAC) index scores | The WOMAC™ Index is a disease-specific, tri-dimensional self-administered questionnaire, for assessing health status and health outcomes in osteoarthritis of the knee and/or hip. | Pain subscale 0-100 |
| | | Stiffness subscale 0-100 |
| | | Function subscale 0-100 |
| Visual Analogue Scale (VAS) | VAS is a continuous scale comprised of a horizontal or vertical visual analog scale usually 10 cm or 100 mm length [both the gradations are used]. It is anchored by two verbal descriptors, one for each symptom extreme. | 0-100mm |
| Lequesne Index of Severity | Composite index assessing pain and disability | 0-24 points |

When examining the performance measurements of the devices reviewed in this clinical evaluation report, it can be seen that all performance data collected in relation to Fermathron and Fermathron plus is comparable to equivalent intra-articular hyaluronic acid viscosupplementation devices.

### 6.1.9 Conclusion on performance

The evaluated clinical studies demonstrate the use of the Fermathron and Fermathron plus to be beneficial in the treatment of pain and stiffness of the knee, hip, ankle and shoulder (Fermathron only) joints in patients with mild to moderate arthritis resulting from degenerative and traumatic changes to the synovial joint. In addition, the assessed data from equivalent devices, Hyalgan and Orthovisc, substantiate the safety and intended use of Fermathron and Fermathron plus. Collectively the data demonstrate that all products under evaluation perform as intended by the manufacturer and safely function as an intra-articular hyaluronic acid viscosupplement.

Overall, sufficient evidence was available to support and demonstrate every intended performance. The performance of the device was demonstrated and is in compliance with the MDD ER3.

## 6.3 Requirements on acceptable benefit/risk profile

### 6.3.1 Overview of the benefits

Fermathron and Fermathron plus are indicated for the relief of pain and stiffness of the knee, hip, ankle and shoulder (Fermathron only) joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint. The duration of effect in patients with mild to moderate osteoarthritis of the knee joint is up to six months. Duration of effect in the hip, ankle and shoulder joints has not been demonstrated.

Viscosupplementation involves the intra-articular injection of hyaluronic acid (HA) after aspiration of any existing joint effusion. The HA injection is intended to replenish the normal synovial fluid viscoelastic properties, however this hypothesis is yet to be fully proven. A systematic review by Rutjes (2012) which analysed 89 trials involving 12,667 adults showed that viscosupplementation moderately reduced OA pain and 17 trials showed a clinically irrelevant effect size. A review by Zychowicz (2014) further supports the benefits of viscosupplementation and suggests that they are a safe and effective method of improving function and alleviating osteoarthritic knee pain for up to 26 weeks.

### 6.3.2 Overview of the risks

An evaluation of the risks is provided in Table 14, looking in particular at the nature and severity of the risks, the probability for a patient to experience a risk, and whether the event causes temporary minor harm or permanent harm. Note that this section is not about complications (or side-effects), these are evaluated in section 6.5.

## Table 14: Summary of the device risks

| Nature | Severity (2=none; 4=limited; 6=moderate; 8=severe, 10=life threatening) | Probability / frequency (2=remote; 4=rare; 6=occasional; 8=frequent, 10=continuously occurring) | Duration Temporary / permanent |
|---|---|---|---|
| **Risks identified through the risk analysis** | | | |
| Product is used for patients with severe arthritis | 8 | 2 | Temporary |
| Product is used for patients without arthritis, possibly presenting with symptoms of another condition | 8 | 2 | Temporary |
| Product is used in joints other than knee, hip, shoulder or ankle (off-label use) | 8 | 2 | Temporary |
| Product is injected into surrounding tissues rather than synovial joint. | 8 | 2 | Temporary |
| Product is used by a person who is not a Healthcare Professional and/or not trained in the procedure of intra-articular injection | 8 | 2 | Temporary |
| Product used after blister seal damaged so syringe & possibly viscosupplement no longer sterile | 10 | 2 | Temporary |
| User removes syringe from blister tray but injection procedure is delayed. Previously sterilised outer surface of syringe could come into contact with bioburden prior to use in patient. | 10 | 2 | Temporary |
| Product used after storage outside required conditions causing product to degrade. | 8 | 4 | Temporary |
| Healthcare professional uses needle which is not compatible with syringe or viscosity of product (e.g. inappropriate gauge) which causes needle detachment or difficulty of injection. | 6 | 2 | Temporary |
| Inappropriate use: Too many injections given or user administers too much solution from that supplied | 8 | 4 | Temporary |
| Too few injections given or user administers insufficient solution from that supplied | 6 | 4 | Temporary |
| Infection at injection site prior to injection or injection site/needle used not clean and bacteria introduced | 10 | 4 | Temporary |
| Intra-articular injection results in pain and swelling at injection site | 6 | 4 | Temporary |
| Product contains sodium hyaluronate which could induce a hypersensitivity reaction. Immunological & pyrogenic response | 6 | 4 | Temporary |
| Use in pregnant or lactating women despite compatibility being unknown | 10 | 2 | Temporary |
| Use in children despite effects on growing joints being unknown | 10 | 2 | Temporary |
| Use with other substances for intra-articular injection despite compatibility being unknown | 8 | 4 | Temporary |
| Joint effusion, if present, is not aspirated prior to injection of product. Insufficient space within joint to allow full administration of does. | 8 | 4 | Temporary |
| Use after product expiry date - possibility that product is no longer sterile or performance impacted | 10 | 4 | Temporary |

| | | | |
|---|---|---|---|
| Multi-use of syringe or needle leading to cross-contamination | 10 | 4 | Temporary |
| Re-sterilisation of syringe leading to inadequate product performance (decrease in viscosity) | 8 | 4 | Temporary |
| Incorrect syringe or needle disposal | 10 | 2 | Temporary |

There are few risks associated with the use of Fermathron and Fermathron plus. As with all intra-articular viscosupplements, a common side effect is a transient pain and swelling at the injection site. Rarely an inflammatory reaction, septic arthritis, or arthralgia could occur which may or may not be associated with Fermathron as is clearly stated in the Instructions for Use.

In addition to the contraindications and potential complications, the Instructions for Use include warnings about the handling and storage of Fermathron and Fermathron plus, reminding surgeons not to re-use the product.

Possible risks relating to impurity or contamination of the material are not within the scope of clinical investigation and have been dealt with adequately by the manufacturer.

In summary, the manufacturer's product literature and Instructions for Use are consistent with the clinical data and cover all the hazards and other clinically relevant information that may impact on the use of the device.

### 6.3.3 Evaluation of acceptability of the benefit / risk profile

The clinical studies evaluated show that many authors find that the use of intra-articular hyaluronic acid for the viscosupplementation of mild to moderate osteoarthritic knee, hip, ankle or shoulder joints (Fermathron only) to be beneficial. Some studies show scepticism of the benefits, and authors suggest that intra-articular corticosteroids, placebos or oral NSAIDSs are equally beneficial. However as the agents have become more widely investigated and understood, viscosupplements have become established as important tools to alleviate pain and stiffness in patients with osteoarthritis resulting from degenerative and traumatic changes to the synovial joint .

The material used in the manufacture of this device, sodium hyaluronate, has a long history of use and is highly biocompatible and non-toxic to the synovial joint.

All clinical studies show the occurrence of similar adverse effects such as transient pain and swelling following intra-articular injections which may occur in up to 20% of patients, although severe local inflammation, warmth and joint effusion are rare (Chen et al., 2002) and is detailed further in section 6.1. Further Risk / benefit analysis for each hazard undertaken in accordance with BS EN ISO 14971:2012 identified and confirmed that each risk was acceptable when weighed against the benefit to the patient when Fermathron is used as intended.

There are many varieties of performance measurements in the treatment of joint osteoarthritis as detailed in section 6.2, including the WOMAC index, the Visual Analogue Scale (VAS) and the Lequesne index of severity, among others. Using these measurements in the performance of the devices examined in this clinical evaluation report, it can be seen that all performance data collected in relation to Fermathron and Fermathron plus is comparable to equivalent intra-articular hyaluronic acid viscosupplementation devices.

The performance and safety of the devices have been established through an acceptable level of clinical data. Taken as a whole the evidence is robust and consistent. The clinical studies investigated an adequate number of patients, who were followed up for an acceptable length of time. The studies were appropriately designed to observe and assess the performance and likely complications.

There is sufficient robust clinical data to conclude that the comparative intra-articular hyaluronic acid viscosupplements assessed in this report perform as intended and with an acceptable level of risk when used as indicated.

It can be assumed that the devices under evaluation Fermathron and Fermathron plus can achieve at least the same level of safety and performance as equivalent devices Hyalgan and Orthovisc, and the comparator devices when used as indicated. It has been demonstrated that intra-articular hyaluronic acid viscosupplements achieve their intended performance during normal conditions of use and that the known and potential risks and adverse events can be minimised and are acceptable when balanced against the expected benefits. The performance and safety of the devices are supported by suitable evidence.

The device literature, essentially the IFU, describes appropriately the intended use supported by sufficient clinical evidence. In addition, the IFU contains all the important information to reduce the risk of use error, information on residual risks and their management.

Overall, the benefit/risk profile of Fermathron and Fermathron plus when used as intended is compatible with a high level of protection of health and safety, and in compliance with the MDD ER1.

# 6.4 Requirements on acceptability of side-effects

Various clinical data either held by the manufacturer (clinical trial reports, internal complaints analysis, CAPAs analysis) or identified through literature search (peer-reviewed papers, adverse events from external databases) were used to detect possible undesirable side-effects and their frequency.

Unwanted post-injection side effects include mild pain or swelling at the injection site, which may occur in up to 20% of patients, however severe local inflammation, warmth and joint effusion are rare (Chen et al. 2002). The same study reported a series of 6 cases were granulomatous inflammation of the synovium occurred after IA-HA administration although it is not known which part of the injection solution was the pathological agent. Aseptic arthritis is another possible side-effect which can develop quickly after the injection, calcium crystal shedding has been used to explain this complication. Anti-inflammatory therapy can be used to relieve the symptoms of aseptic arthritis (Roos et al. 2004).

Complaints relating to Fermathron and Fermathron plus are very rare and form a very small percentage of the number of items sold each year. The most common complaint reported related to inflammation. This is a known risk for viscosupplementation with HA and rates reported for Fermathron and Fermathron plus were

well within incidence levels reported for similar products within the literature (e.g. 1.2% severe joint pain and swelling for Hyalgan in PMA study). There is no evidence of consistent failure or problems with the product.

Overall, the identified side-effects were acceptable when compared to the product benefit and Fermathron and Fermathron plus is compliant with the MDD ER6.

# 7. CONCLUSIONS

The aim of this clinical evaluation was to review the clinical performance and safety of Fermathron and Fermathron plus and to evaluate its benefit / risk profile according to the MEDDEV 2.7.1 Rev. 4. Fermathron and Fermathron plus are intended for the relief of pain and stiffness of the knee, hip, ankle and shoulder (Fermathron only) joints in patients with mild to moderate osteoarthritis resulting from degenerative and traumatic changes to the synovial joint.

Performance and safety of the device have been demonstrated using published, peer-reviewed literature, clinical trial reports for Fermathron and for equivalent products and complaints reports. The database PubMed was searched for relevant literature, identified papers were obtained and analysed. In total, the set of data selected and appraised was considered robust and consistent. The clinical studies investigated an adequate number of patients with an acceptable follow-up time. The studies were also appropriately designed to observe and assess performance and likely complications.

### Summary of performance

The performance of intra-articular hyaluronic acid devices for viscosupplementation has been reported extensively in the literature. Earlier sections in this report confirm that Fermathron and Fermathron plus and their equivalent devices are capable of meeting their stated objectives to act as viscosupplements to relieve the symptoms of mild to moderate osteoarthritis in the ankle, knee, hip or shoulder (Fermathron only) joints.

Overall, sufficient evidence was available to support and demonstrate every intended performance. The performance of the device has been demonstrated and in compliance with the MDD ER3.

### Summary safety

Patient numbers and follow-up were adequate to determine if the devices were acting as intended and to observe the emergence of adverse events and complications. Taken as a whole, the body of data for each device is of sufficient quality and relevance to enable conclusions to be drawn about the performance and safety of the devices.

Overall, sufficient evidence was available to support and demonstrate every intended safety aspect. The safety of the device has been demonstrated and in compliance with the MDD ER1.

### Risk / benefit analysis

The device literature, essentially the IFU, appropriately describes the intended use and is supported by sufficient clinical evidence. In addition, the IFU contains all the important information to reduce the risk of use error, as well as residual risks and their management.

Overall, the identified side-effects are an acceptable risk when compared to product benefit and therefore compliance with MDD ER6 has been demonstrated. The benefit/risk profile of Fermathron and Fermathron plus, when used as intended, is compatible with a high level of protection of health and safety and is in compliance with the MDD ER1.

**Necessary PMS procedures**

As for any medical device, Fermathron and Fermathron plus will be subject to ongoing Post Market surveillance according to QOP Q157 to collect and analyse new inputs regarding its safety and performance and to continuously analyse the benefit / risk profile.

No post-market clinical follow-up is necessary to demonstrate the intended purpose of Fermathron and Fermathron plus, its good performance and safety or the conformity to essential requirements. This decision is based on the following:

No change to risk/benefit profile or new risks have been identified

There are no significant changes to the product or its intended use

The device has been in long term use and is based on well established technology

Sufficient clinical data supports the performance and safety of Fermathron and Fermathron plus, including the clinical study originally performed by McDonald et al (2000) comparing Fermathron and Hyalart (Hyalgan) in the treatment of knee osteoarthritis. In addition, published data from the equivalent devices Hyalgan and Orthovisc supports the safety and performance of both devices.

Note that this decision will be reviewed in line with new requirements and strategy for the European Medical Device Regulation 2017-745.

**Date of the next evaluation:**

The next update must be completed by December 2020 in line with PMS procedures however if new information is received that has the potential to change the conclusions of the CER then an earlier update may be carried out.

# 8. DATES, QUALIFICATIONS AND SIGNATURES OF THE RESPONSIBLE EVALUATORS

The following evaluators have participated to the writing, reviewing and approbation of the report and agree with its content.

**Table 15: Date, qualification and signature of responsible evaluators**

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| **Author of the report** | **Name** | Emma McColm | **Position** | External Regulatory Affairs Consultant |
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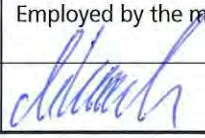
| | **Date** | 18/09/2018 | **Signature** |  |
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| | **Degree(s) / years of experience in the field** | MD, BSc Physics / 30 yrs | **Declaration of interest** | External evaluator receiving benefits from the manufacturer |
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# 10. List of Annexes

Annex 1: Literature search, appraisal and report

**Declaration of interests and CVs of evaluators are held on file by Hyaltech.**