Summary of Safety and Clinical Performance

Hyaluronidase in FertiCult Flushing medium

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device. The SSCP is not intended to replace the Instructions For Use (IFU) as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to the intended users.

1 Device identification and general information

1.1 Device trade name(s)

Hyaluronidase in FertiCult Flushing medium

1.2 Manufacturer's name and address

FertiPro NV
Industriepark Noord 32
8730 Beernem
Belgium

1.3 Manufacturer's single registration number (SRN)

BE-MF-000000313

1.4 Basic UDI-DI

5411967HYA13K

1.5 Medical device nomenclature description/text

Applicable EMDN code: U08020502 (Materials/solutions for preparation/handling for assisted reproduction)

1.6 Class of device

Class III devices according to Annex VIII of the MDR (Regulation (EU) 2017/745).

1.7 Year when the first certificate (CE) was issued covering the device

CE marking of Hyaluronidase in FertiCult Flushing medium: 2015

1.8 Authorized representative if applicable; name and the SRN

Not applicable.

1.9 NB's name and single identification number

BSI Group The Netherlands BV
NB identification number: 2797

2 Intended use of the device

2.1 Intended purpose

Hyaluronidase in FertiCult Flushing medium is used in the oocyte denudation process for the digestion of the hyaluronic acid between cumulus cells in preparation of intra cytoplasmic sperm injection (ICSI).

2.2 Indication(s) and intended patient groups

Before fertilization, the oocyte is surrounded by the corona radiata and scattered parts of cumulus cells. The hyaluronic acid in the intercellular matrix makes the fluid that surrounds those cells sticky and stringy. In vivo, enzymes like hyaluronidase are released by the acrosome reaction of the sperm cells and dissolve the intercellular matrix between the cumulus cells. This way, the throng of cumulus cells is loosened and more and more sperm cells are able to bind to the pellucid zone and undergo the subsequent acrosome reaction.

The European Society of Human Reproduction and Embryology (ESHRE) recommends to use an enzymatic procedure with hyaluronidase, followed by mechanical denudation using a pipette, for the removal of cumulus and corona cells. Hyaluronidase in FertiCult Flushing medium is designed for this purpose and contains 80IU/ml hyaluronidase in FertiCult Flushing medium. This medium is typically used in the oocyte denudation process for the digestion of the hyaluronic acid between cumulus cells.

Direct physical contact occurs between the media products and the human oocyte. The medium does not come into contact with the human body.

Hyaluronidase in FertiCult Flushing medium is used in specialized laboratories performing fertilization techniques, including IVF and ICSI. The intended users are IVF professionals (lab technicians, embryologists, or medical doctors).

2.3 Contraindications and/or limitations

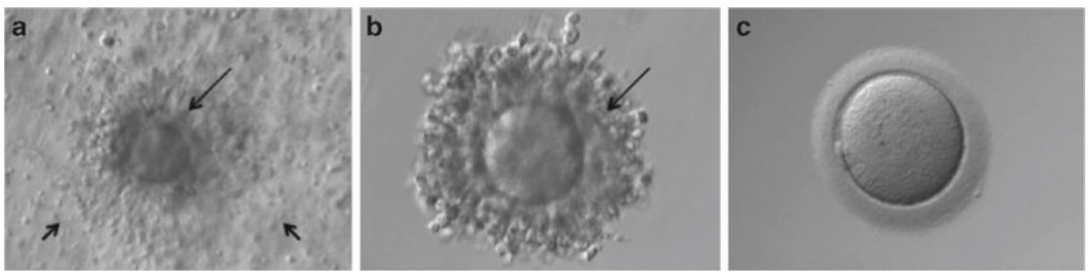
There are no reasonably foreseeable medical conditions for which Hyaluronidase in FertiCult Flushing medium is not to be used.

3 Device description

3.1 Description of the device

Hyaluronidase in FertiCult Flushing medium is a device used to facilitate the oocyte denudation process. The hyaluronidase is an enzyme derived from bovine testes and is capable of hydrolysing hyaluronic acid, the latter being one of the most abundant constituents of the extracellular matrix of the oocyte. When collected, each oocyte is surrounded by a matrix of cells called the cumulus-oocyte complex (COC). The COC is composed of cumulus granulosa cells embedded in a matrix of long hyaluronan oligosaccharide chains cross-linked by a complex of hyaluronan binding cell surface and extracellular matrix proteins and proteoglycans. In vivo, enzymes like hyaluronidase are released by the acrosome reaction of the sperm cells and dissolve the intracellular matrix between the cumulus cells. Also in vitro during ICSI procedures, COC around oocytes are removed (i.e. “oocyte denudation”). For that purpose, it is generally accepted to use an enzymatic procedure with hyaluronidase, which facilitates the subsequent mechanical denudation process using a pipette (see below).

Figure: Oocyte denudation steps. (a) Oocyte surrounded by corona radiata (short arrow) and cumulus cells (long arrow); (b) oocyte after the enzymatic-induced dispersion of cumulus cells; (c) MII denuded oocyte (Figure from (Ebner 2012))



Hyaluronidase in FertiCult Flushing medium is a ready-to-use formulation used for oocyte denudation. The medium contains 80 IU/ml hyaluronidase and is based on the composition of FertiCult Flushing medium (manufactured by FertiPro and CE marked as class III device).

Hyaluronidase in FertiCult Flushing medium contains Human Serum Albumin (HSA). The inclusion of Human Serum Albumin (which is a medicinal substance derived from human blood plasma) in ART media from FertiPro is approved by the EMA (European Medicine Agency).

The hyaluronidase used in the device is derived from bovine testis and is certified with a TSE risk evaluation Certificate of Suitability (CEP).

The device is not intended for single use. Multiple single-procedures can be performed with one bottle of Hyaluronidase in FertiCult Flushing medium. The media can be used up to 7 days after bottle opening (when sterile conditions are maintained and the products are stored at 2-8°C).

Hyaluronidase in FertiCult Flushing medium is sterilized using aseptic processing techniques (filtration).

3.2 A reference to previous generation(s) or variants if such exist, and a description of the differences

No previous generation of the device has been brought on the market by FertiPro.

3.3 Description of any accessories which are intended to be used in combination with the device

No accessories for Hyaluronidase in FertiCult Flushing media are identified.

3.4 Description of any other devices and products which are intended to be used in combination with the device

Mineral Oil (e.g. FertiCult™ Mineral Oil/ FertiCult™ High Viscosity Oil) and washing medium (e.g. FertiCult™ Flushing medium.

4 Risks and warnings

4.1 Residual risks and undesirable effects

1. The first remaining residual risk is the inclusion of HSA in Hyaluronidase in FertiCult Flushing medium. The inclusion of this medicinal substance derived from human blood plasma in the devices is approved by the EMA. A potential risk associated with HSA is the transmission of viral or prion-carried diseases and the batch-to batch variation:

    - **Batch-to-batch variation** is still a problem because of the inherent variability in donor blood. Due to this fluctuation, standardization of procedures remains difficult.

        - ↔ For this reason, a mouse embryo assay are routinely performed as part of the batch release criteria

    - Secondly; with the use of a human-derived protein source, a potential risk exists of **transmitting viral or prion-carried diseases**.

        - ↔ HSA is manufactured with a pasteurization procedure that has led to an excellent viral safety record over the 50 years of clinical use. Only Plasbumin-25 or alternatively, Albunorm 25 will be used as a source of albumin, as these products are covered by a valid Plasma Master File, and the EMA has positively evaluated the usefulness, safety and benefit of the inclusion of these products in FertiPro ART-media.

↔ On the other hand, despite the rigorous quality controls, all cell culture media should still be treated as potentially infectious. At present, there is no known test method that can offer full assurance that products derived from human blood will not transmit infectious agents. Direct physical contact occurs between Hyaluronidase in FertiCult Flushing medium and the human sperm cell. The instructions for use / MSDS clearly warn that the medium contains human albumin solution and that protective clothing should be worn.

The major benefit of HSA in Hyaluronidase in FertiCult Flushing medium is clear:

- pH regulator
- Osmotic regulator
- Stabilizator of cell membrane
- Nutrient and carrier of growth promoting substances (i.e. amino acids, vitamins, fatty acids, hormones, growth factors)
- Scavenger (of for example toxins and waste products from cell metabolism)
- Surfactant (anti-adhesion), thereby facilitating gamete and embryo manipulation

Based on the analysis it is concluded that the benefit of adding HSA to the media outweighs the risk and the overall residual risk related to the use of Hyaluronidase in FertiCult Flushing medium with inclusion of HSA has been judged acceptable.

2. The second remaining residual risk is the inclusion of bovine testes derived hyaluronidase in Hyaluronidase in FertiCult Flushing medium. This implicates an increased risk for contamination of the medium with:
    1) Parasites and unclassified pathogenic entities
    2) Bacteria, moulds and yeasts
    3) TSE agents
    4) Viruses

    Points 1) and 2) are reduced to an acceptable level due to appropriate and validated production processes, which include proper in-coming inspections on the hyaluronidase raw material (endotoxin testing), in-process controls (bioburden tests), sterile filtration, and quality controls on the finished medical devices (sterility test, endotoxins).

    Point 3) on the risk on TSE transmission is reduced to an acceptable level by using an EDQM certified hyaluronidase as raw material. This risk analysis has addressed all factors required by the relevant regulations concerning TSE risk management. Based on the WHO tables on tissue infectivity distribution in TSE and ISO22442-1, bovine testis is classified as tissue with no detectable infectivity. Risk reduction was performed at the level of selecting source material (which includes species, geographical origin, health status and feeding of animals, veterinary control) for minimal contamination with TSE agents, as well as on the level of collection, storage and transport of the testis.

    Point 4) on the risk for virus transmission is mainly reduced by appropriate selection of source material (which includes species, geographical origin, health status and feeding of animals, veterinary control). In addition, viral removal / inactivation steps are implemented in the manufacturing process of the raw material.

    In addition to this, FertiPro evaluates annually on the presence of ruminant zoonoses in source countries, and the possible impact for safe use of bovine derived raw material in medical devices.

Based on the analysis it is concluded that the residual risks associated with the incorporation of bovine testes derived hyaluronidase are therefore considered acceptable.

With respect to the above described residual risks, following information is provided to the customer:

- Product composition is clearly indicated on the labels and instructions for use
- Instructions for use contains the following warning:
  - Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. There are no reports of proven virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes. Therefore, handle all specimens as if capable of transmitting HIV or hepatitis.
  - All blood products should be treated as potentially infectious. Source material used to manufacture this product was tested and found non-reactive for HbsAg and negative for Anti-HIV-1/-2, HIV-1, HBV, and HCV. Furthermore, source material has been tested for parvovirus B19 and found to be non-elevated. No known test methods can offer assurances that products derived from human blood will not transmit infectious agents.
  - The hyaluronidase used in this product is derived from bovine testis and is certified with a transmissible Spongiform Encephalopathy (TSE) risk evaluation Certificate of Suitability (CEP). The animals from which the hyaluronidase is derived, are determined “fit for human consumption” and originate from countries with “negligible BSE risk”, as determined in Resolution “Recognition of the Bovine Spongiform Encephalopathy Risk Status of Member Countries”, adopted by the World Organisation for Animal Health (OIE). According to the World Health Organization (WHO) guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies (2010) and ISO22442-1, testes from bovine source are classified as “Tissues with no detected infectivity”.

4.2 Warnings and precautions

Besides the above, attention should be paid to the following warnings and precautions (as described in the instructions for use):

- Do not use the product if:
  - it becomes cloudy or shows any evidence of microbial contamination
  - seal of the container is opened or defect when the product is delivered
  - expiry date has been exceeded
- Do not freeze before use
- Keep away from (sun)light
- Do not re-sterilize after opening
- Aseptic technique should be used to avoid possible contamination.
- Always wear protective clothing when handling specimens.
- Depending on the number of procedures that will be performed on one day, remove the required volume of medium under aseptic conditions in an appropriate sterile recipient. This is in order to avoid multiple openings/warming cycles of the medium. Discard excess (unused) media.

- Any serious incident (as defined in European Medical Device Regulation 2017/745) that has occurred should be reported to FertiPro and the competent authority of the Member State in which the user and/or patient is established.

4.3 Summary of any field safety corrective action (FSCA including FSN) if applicable

In 2021, one IVF clinic in the EU reported a serious incident related to Hyaluronidase in FertiCult Flushing medium. A field safety corrective action was started in which FertiPro requested to return the concerned batch Hyaluronidase in FertiCult Flushing medium present at the IVF clinic. As the incident appeared an isolated, customer-specific issue, no field safety corrective action for the complete batch was required. FertiPro performed additional and throughout investigations on the concerned batch Hyaluronidase in FertiCult Flushing medium that was returned form the IVF center as well as on bottles retained at FertiPro: no problems with the concerned lot Hyaluronidase in FertiCult Flushing could be detected. Applicable reporting to the authorities/Notified Body was performed and closed as such.

5 Summary of clinical evaluation and post-market clinical follow-up (PMCF)

5.1 Real-world evidence analyses

A literature search is performed to investigate whether embryological or clinical ART outcomes obtained during literature search are higher than the embryological minimal competency limits or are within the range of the clinical ART outcomes described in the benchmark papers from the ESHRE (see tables below).

The Vienna consensus report published in 2017 is the result of a 2 day consensus meeting of expert professionals from Sweden, Turkey, UK, Australia, Italy, Spain, Belgium, Austria, Ireland, Canada, USA, and Norway. As a starting point for the discussion, two surveys were organized to collect information on indicators used in IVF laboratories worldwide. During the meeting, the results of the surveys, scientific evidence (where available), and personal clinical experience were integrated into presentations by experts on specific topics. After presentation, each proposed indicator was discussed until consensus was reached within the panel (ESHRE Special Interest Group of Embryology 2017).

The following minimal competency limit concerning embryological outcomes is reported by the expert group:

Minimal competency limits reported by the ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine in 2017. The Vienna consensus: report of an expert meeting on the development of art laboratory performance indicators (ESHRE Special Interest Group of Embryology 2017)	ICSI normal fertilization rate: **≥65%** *(lower range: 55%)*

Each year, the ESHRE publishes a peer-reviewed report, which collects, analyses and reports ART data generated in Europe. The most recent report includes data from 1422 institutions in 39 countries, with a total of 1 007 598 treatment cycles (covering the time period from 1 January to 31 December 2018). (Wyns et al. 2022) and data is summarized in the table below.

ART in Europe, 2018: results generated from European registries by ESHRE (Wyns et al. 2022) A total of 1 007 598 treatment cycles, involving 162 837 with IVF, 400 375 with ICSI, 309 475 with frozen embryo replacement (FER), 48 294 with preimplantation genetic testing (PGT), 80 641 with egg donation (ED), 532 with IVM of oocytes and 5 444 with FOR (frozen oocyte replacement) were recorded.	**Intra cytoplasmic sperm injection (ICSI):** Clinical pregnancy rate per aspiration: 24.9% *(range:* 13.8 – 37.3%) Clinical pregnancy rate per transfer: 35.3% *(range:* 14.8 – 58.3%) Delivery rate per aspiration: 18.5% *(range:* 8.7 – 31.3%) Delivery rate per transfer: 26.2% *(range:* 9.3 – 37.3%)

The articles studying the performance of Hyaluronidase in FertiCult Flushing medium are indicated in the table below. Overall, it can be concluded from these papers that embryological and/or clinical ART outcomes when Hyaluronidase in FertiCult Flushing medium is used for enzymatic oocyte denudation are consistent with the embryological minimal competency limits (ESHRE Special Interest Group of Embryology 2017) or are consistent with the published outcomes as reported by the ESHRE(Wyns et al. 2022), suggesting a safe and adequate performance of Hyaluronidase in FertiCult Flushing medium.

5.2 Real world evidence analyses

A literature search is performed to investigate whether embryological and clinical ART data (pregnancy and delivery rates) obtained during the search fall within the range of the outcomes described in the benchmark data. There were 20 papers retrieved in literature studying the performance of Hyaluronidase in FertiCult Flushing medium. It can be concluded from these papers that embryological and clinical ART outcomes, when Hyaluronidase in FertiCult Flushing medium is used, fall within the range of the outcomes described in the benchmark papers, suggesting a safe and adequate performance of Hyaluronidase in FertiCult Flushing medium.

5.3 Device registers

In addition, clinical data is obtained from IVF centers in Europe that use Hyaluronidase in FertiCult Flushing medium. ART outcomes of these clinics are consistent with clinical outcomes described in national public registers of the countries in which the IVF centers are located or are consistent with the ART outcomes as reported by the benchmark papers.

5.4 Analysis complaint, customer/market feedback, vigilance

No additional actions were initiated, based on the cumulative nature and/or occurrence of all complaints, customer/market feedback and vigilance (if any) during the PMCF analysis.

Since CE-marking, there was one Field Safety Corrective Action (FSCA) in 2021. This FSCA was an isolated, customer-specific issue where some bottles of the concerned batch of Hyaluronidase in FertiCult Flushing medium were returned to FertiPro. FertiPro performed additional and thorough investigations on the concerned batch Hyaluronidase in FertiCult Flushing medium that was returned from the IVF center as well as on bottles retained at FertiPro. No problems with the concerned lot Hyaluronidase in FertiCult Flushing could be detected. Applicable reporting to the authorities/Notified Body was performed and closed as such.

5.5 An overall summary of the clinical performance and safety

From the clinical evaluation report and PMCF, one can conclude that Hyaluronidase in FertiCult Flushing medium functions as stated by the manufacturer: i.e. medium that can be used oocyte denudation.

This is established by clinical data obtained during literature search which demonstrate that embryology outcomes of procedures in which Hyaluronidase in FertiCult Flushing medium is used, are consistent with the minimal competency limits reported by the Vienna consensus group (ESHRE Special Interest Group of Embryology 2017) or by ART results from literature which indicate that ART outcomes of procedures in which Hyaluronidase in FertiCult Flushing medium is used are consistent with the

published outcomes as reported by ESHRE (Wyns et al. 2022). In addition, clinical data from IVF centers show that ART outcomes of procedures in which Hyaluronidase in FertiCult Flushing medium is used, are consistent with published national ART outcomes in the country where the IVF clinic is located or are consistent with the published outcomes as reported by the national average values or the ESHRE(Wyns et al. 2022).

Moreover, there is no evidence from the clinical data, as well as from the registered complains, market/customer feedback and/or vigilance that Hyaluronidase in FertiCult Flushing medium is toxic for gametes and embryos, nor that the media have risk for mutagenity, oncogenicity, teratogenity, carcinogenity, cytotoxicity, allergenicity and irritancy for patients and users. These data further suggest that the benefit risk ratio of Hyaluronidase in FertiCult Flushing medium remains acceptable.

5.6 Ongoing or planned post-market clinical follow-up

Post-market clinical follow-up for Hyaluronidase in FertiCult Flushing medium (including PMCF for the HSA included in the medium) will be performed at least yearly and will include analyses of real-world evidence by performing a literature search, screening of device registers for clinical data, as well as analysis of all complaints, customer/market feedback, vigilance.

This Summary of Safety and Clinical Performance will be updated with information from the post-market clinical follow-up, if this is needed to ensure that any clinical and/or safety information described in this document remains correct and complete.

6 Possible diagnostic or therapeutic alternatives

Several devices as Hyaluronidase in FertiCult Flushing medium with a similar intended use are available on the European Union or international markets. Besides these, there are no other alternative treatments that can be used for enzymatic oocyte denudation.

7 Suggested profile and training for users

Hyaluronidase in FertiCult Flushing media are used in specialized laboratories performing fertilization techniques, including IVF, ICSI and sperm preparation / analysis. The intended users are IVF professionals (lab technicians, embryologists, or medical doctors).

8 Reference to any applicable common specification(s), harmonized standard(s) or applicable guidance document(s)

The following guidance document was used for compilation of the SSCP:

- **MDCG 2019-9**: Summary of safety and clinical performance A guide for manufacturers and notified bodies (August 2019).

The following technical standards apply to Hyaluronidase in FertiCult Flushing medium:

- **MDR 2017/745**: European Medical Device Regulation 2017/745 of 5 April 2017.
- **ISO 13485:2016 / EN ISO13485:2016 (Amd 11:2021)**:: Medical devices — Quality management systems — Requirements for regulatory purposes.
- **ISO 10993-1:2018/EN ISO 10993-1:2020**: Biological evaluation of medical devices -- Part 1: Evaluation and testing.
- **ISO 10993-18:2020/Amd 1/2022 / EN ISO 10993-18:2020**: Biological evaluation of medical devices – Part 18: Chemical characterization of medical device materials within a risk management process
- **ISO 13408-1:2008 (Amd 1:2013)/EN ISO 13408-1:2015**: Aseptic processing of health care products – Part 1: general requirements.

- **(EN) ISO 13408-2:2018**: Aseptic processing of health care products – Part 2: Filtration.
- **(EN) ISO 13408-6:2021**: Aseptic processing of health care products – Part 6: Isolator systems.
- **(EN) ISO 14644-1:2015**: Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration.
- **(EN) ISO 14644-3:2019**: Cleanrooms and associated controlled environments - Part 3: Test methods.
- **ISO 14971:2019/EN ISO 14971:2019 (Amd 11:2021)**: Medical devices – Application of risk management to medical devices.
- **(EN) ISO 15223-1:2021**: Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements.
- **(EN) ISO 17665-1:2006**: Sterilization of health care products – Moist heat – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices.
- **(EN) ISO 20417:2021:** Information to be supplied by the manufacturer
- **(EN) ISO 22442-1: 2020**: Medical devices utilizing animal tissues and their derivatives: Part 1: Application of risk management
- **(EN) ISO 22442-2: 2020**: Medical devices utilizing animal tissues and their derivatives: Part 2: controls on sourcing, collection and handling
- **(EN) ISO 22442-3: 2007**: Medical devices utilizing animal tissues and their derivatives: Part 3: validation of the elimination and/or inactivation of viruses and TSE agents
- **ISO 23640:2011/EN ISO 23640:2015**: In vitro diagnostic medical devices: Evaluation of stability of in vitro diagnostic reagents (Applicable with exclusion of the following sections: No standard is available for the evaluation of stability of Medical Devices, therefore this standard is used as guideline for the set-up of the stability testing)
- **EN 556-2:2015**: Sterilization of medical devices – Requirements for medical devices to be designated 'STERILE' –Requirements for aseptically processed medical devices.
- **IEC 62366-1:2015 (Amd 1:2020)**: Medical devices - Part 1: Application of usability engineering to medical devices.
- **NBOG BPG 2014-3**: Guidance for manufacturers and Notified Bodies on reporting of Design Changes and Changes of the Quality System.
- **EMA/CHMP/578661/2010**: EMA recommendation on the procedural aspects and dossier requirements for the consultation to the EMA by a notified body on an ancillary medicinal substance or an ancillary human blood derivate incorporated in a medical device or active implantable medical device.
- **Commission Regulation No 722/2012**: Commission Regulation No 722/2012 of August 2012 concerning particular requirements as regards the requirements laid down in Council Directives 90/385/EEC and 93/42/EEC with respect to active implantable medical devices and medical devices manufactured utilizing tissues of animal origin.

9 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.1	11/12/2020	Initial version	Date: not yet Validation language: English
A.2	22/06/2021	Update 2021 BSI conformity assessment round 1	Date: not yet Validation language: English
A.3	17/08/2021	BSI conformity assessment round 2	Date: 27/02/2023 Validation language: English

A.4	03/06/2022	Update 2022: addition PMCF data	Not submitted for validation, as there were no significant changes that required validation.
A.5	08/09/2023	Update 2023: addition PMCF data	Not submitted for validation, as there were no significant changes that required validation.

10 Summary of the safety and clinical performance of the device intended for patients

A summary of the safety and clinical performance of the device intended for patients, is not applicable as the device is for professional use only.

11 References

Ebner, T. 2012. 'oocyte treatment and preparation for microinjection.' in, *Practical manual on in vitro fertilization*.

ESHRE Special Interest Group of Embryology, ESHRE. 2017. 'The Vienna consensus: report of an expert meeting on the development of art laboratory performance indicators', *Hum Reprod Open*, 2017: hox011.

Wyns, C., C. De Geyter, C. Calhaz-Jorge, M. S. Kupka, T. Motrenko, J. Smeenk, C. Bergh, A. Tandler-Schneider, I. A. Rugescu, and V. Goossens. 2022. 'ART in Europe, 2018: results generated from European registries by ESHRE', *Hum Reprod Open*, 2022: hoac022.