Summary of Safety and Clinical Performance

FertiCult Aspiration 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)

FertiCult Aspiration 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

5411967ASPI1V4

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

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

FertiCult Aspiration medium: 2015

1.8 Authorised 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

FertiCult Aspiration medium is a ready-to-use formulation used for oocyte aspiration and flushing the ovarian follicles during oocyte pick-up as part of Assisted Reproductive Technologies (ART) procedures. This medium contains 2.5 IU/ml heparin and is based on the composition of FertiCult Flushing medium without human albumin (manufactured by FertiPro and CE marked as class III device). Heparin is added to the medium to avoid blood clot formation in the tubing during the aspiration and/or flushing of oocytes during ART.

2.2 Indication(s) and intended patient groups

FertiCult Aspiration medium is a cell culture medium for human oocyte pick-up. The purpose of the oocyte collection procedure is to collect oocytes which are then used in In Vitro Fertilization (IVF) and other ART procedures.

The medium is designed to enable oocyte aspiration and flushing of ovarian follicles during ART procedures of patients with infertility problems.

Direct physical contact occurs between the media products and human oocytes and ovarian follicles of the patient during aspiration and/or flushing of the follicles.

2.3 Contraindications and/or limitations

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

3 Device description

3.1 Description of the device

FertiCult Aspiration medium:

- is used for oocyte aspiration and flushing of the ovarian follicles during oocyte pick-up
- is based on the composition of FertiCult Flushing medium without human serum albumin (also manufactured and CE-marked by FertiPro)
- contains 2.5 IU/ml heparin to avoid blood clot formation in the tubing during the aspiration and/or flushing of the oocytes during ART (The added heparin complies with Ph. Eur. Monograph Standard 0333, is EDQM-certified. The inclusion of heparin is submitted for approval by the MEB (Medicine Evaluation Board, competent authority the Netherlands.)

The device is not intended for single use. Multiple single-procedures can be performed with one bottle of FertiCult Aspiration 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).

FertiCult Aspiration 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 devices have 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 FertiCult Aspiration medium are identified.

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

No other specific devices are intended to be used in combination with the device.

4 Risks and warnings

4.1 Residual risks and undesirable effects

As identified in the risk assessment report of the medium, there are no risks that could not be reduced to an acceptable level.

FertiCult Aspiration does contain heparin, which does imply the following:

First, heparin is a medicinal product, which may increase the risk on abdominal bleeding upon oocyte aspiration and follicular flushing. However, risk control measures are taken at the level of design, manufacturing and information for safety and the residual risk is considered acceptable.

Second, heparin is derived from animal tissue (alternative sources are currently not available). As a consequence, a complete elimination of risk at source is not possible but with the risk controls described in the risk assessment report, the use of animal derived heparin in FertiCult Aspiration medium is justified. The risk on viral and TSE transmission is sufficiently reduced by using an EDQM certified heparin as raw material, which is manufactured under GMP conditions (Heparin sodium, LEO Pharma). The heparin is manufactured to comply with all requirements for parenteral use in patients with coagulation disorders. It is extracted and purified from porcine intestinal mucosa. This animal tissue is not classified by the WHO and ISO 22442-1 as a tissue with detectable infectivity. Importantly, there is only a limited contact with patients, as FertiCult Aspiration medium contains only a small amount of heparin (2.5 IU/ml) and there is only short-term exposure during oocyte aspiration and follicular flushing. Therefore, the residual risk is considered acceptable.

Taken together, the overall residual risk related to the use of FertiCult Aspiration medium is acceptable, in view of their intended use as specified in the instructions for use.

In order to disclose the overall risk regarding the incorporation of sodium heparin, the following information is provided to the customer:

- The concentration of heparin is clearly indicated on the labels and instruction for use
- Instructions for use contains the following warnings: "FertiCult Aspiration medium contains heparin which is derived from porcine intestinal mucosa".

No other known undesirable side-effects are identified.

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
- Do not re-sterilize after opening
- 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 opening/warming cycles of the medium. Discard excess (unused) media.
- FertiCult Aspiration medium contains heparin which is derived from porcine intestinal mucosa. The heparin is certified with a Certificate of Suitability (CEP). The animals from which the heparin is derived, are determined "fit for human consumption".
- Aseptic technique should be used to avoid possible contamination.
- All human, organic material should be considered potentially infectious. Handle all specimens as if capable of transmitting HIV or hepatitis.
- Always wear protective clothing when handling specimens.
- 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

No field safety corrective actions with regard to FertiCult Aspiration medium were needed.

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 and/or clinical ART data are consistent with the outcomes as described in the benchmark papers from the ESHRE (European Society of Human Reproduction and Embryology) (see tables below).

The Vienna consensus paper is a report of an expert meeting on the development of ART laboratory performance indicators, reported by the ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine: see (ESHRE Special Interest Group of Embryology 2017).

The following competency limits concerning embryological outcomes are reported by the expert group:

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)	IVF normal fertilization rate: ≥60% (lower range: 50%) ICSI normal fertilization rate: ≥65% (lower range: 55%) Blastocyst development rate: ≥40% (lower range: 30%) ***Since multiple factors can have an influence on the embryology outcomes, (ART policy, approach of the clinic, patients characteristics), a value 10% lower than the competency limit is acceptable.***

Each year, the ESHRE publishes a peer-reviewed report, which collects, analyses and reports ART data generated in Europe. The most recent report (Wyns et al. 2022) 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) and is summarized in the table below:

ART in Europe, 2018: results generated from European registries by ESHRE	**In vitro fertilization (IVF):**	**Intra cytoplasmic sperm injection (ICSI):**	**Frozen embryo transfer (FET):**
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 5444 with FOR (frozen oocyte replacement) were recorded.	Clinical pregnancy rate per aspiration: **26.2%** *(range: 7.8 – 47.2%)* Clinical pregnancy rate per transfer: **35.9%** *(range: 21.1 – 50.5%)* Delivery rate per aspiration:**19.0%** *(range: 6.3 – 27.8%)* Delivery rate per transfer:**26.4%** *(range: 14.2 – 38.7%)*	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%)*	Pregnancy rate per thawing: **34.6%** *(range: 24.4 – 49.5%)* Pregnancy rate per transfer:**35.5%** *(range: 23.4 – 50.4%)* Delivery rate per thawing: **25.2%** *(range: 17.8 – 40.6%)* Delivery rate per transfer: **25.7%** *(range: 17.1 – 41.4%)*
	Since multiple factors can have an influence on the ART outcomes (ART policy, approach of the clinic, patients characteristics), a value within the range of the ESHRE value is acceptable.		

There were 4 articles retrieved in literature studying the performance of FertiCult Aspiration medium. It can be concluded from these papers that embryology and/or ART outcomes, when FertiCult Aspiration medium is used, are consistent with the embryological competency limits (ESHRE Special Interest Group of Embryology 2017) and/or with the published ART outcomes as reported by the ESHRE (Wyns et al. 2022), suggesting a safe and adequate performance of FertiCult Aspiration medium.

5.2 Device registries

In addition to the above, ART outcomes of IVF clinics located in Europe are included in the clinical evaluation report of FertiCult Aspiration medium (data not publicly available). The ART outcomes of the clinics are consistent with the published outcomes of the ESHRE paper (Yearly updated. Most recent report is: (Wyns et al. 2022)), indicating that FertiCult Aspiration medium of FertiPro NV not interferes with the general ART procedure.

5.3 Analysis complaints, 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.

5.4 An overall summary of the clinical performance and safety

FertiCult Aspiration medium for the flushing of the follicles and/or oocyte pick-up have been successfully used for more than 20 years and is considered a standard procedure. Heparin is added to the culture medium in order to avoid blood clot formation in the tubing during the aspiration and/or flushing of oocytes during ART.

In the clinical evaluation report of FertiCult Aspiration medium, it is sufficiently indicated that the incorporation of heparin in a buffer solution used for follicular flushing / oocyte pick-up is justified and without detrimental effects. Also, based on the clinical evaluation report of FertiCult Flushing medium without human albumin (the buffer solution), it is indicated that the product formulation is safe to use for oocytes.

Overall, it can be concluded that FertiCult Aspiration medium functions as stated by the manufacturer. This is established by clinical data, obtained during literature search and from two IVF centers in Europe, which all demonstrate that embryology and/or ART outcomes of procedures in which FertiCult Aspiration medium is used are consistent with the published outcomes as reported by the ESHRE published in the previous year or the same year of that CER update, most recent report are: (Wyns et al. 2022; ESHRE Special Interest Group of Embryology 2017).

Moreover, there is no evidence from the clinical data, as well as from the registered complains, market/customer feedback and/or vigilance that FertiCult Aspiration medium is toxic for gametes and embryos, nor that the medium has a risk for mutagenity, oncogenicity, teratogenity, carcinogenity, cytotoxicity, material-mediated pyrogenicity, allergenicity and irritancy for patients and users.

5.5 Ongoing or planned post-market clinical follow-up

Post-market clinical follow-up for FertiCult Aspiration 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.

The 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

Devices with similar intended use as FertiCult Aspiration medium are available on the European Union or international markets. Besides these media, there are no other alternative treatments that can be used.

7 Suggested profile and training for users

FertiCult Aspiration 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).

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

The following guidance document was used:

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

The following technical standards apply to FertiCult Aspiration 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.
- **(EN) ISO 10993-3:2014:** Biological evaluation of medical devices -- Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.
- **(EN) ISO 10993-5:2009:** Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity.
- **(EN) ISO 10993-9:2021:** Biological evaluation of medical devices -- Part 9: Framework for identification and quantification of potential degradation products.
- **(EN) ISO 10993-10:2023:** Biological evaluation of medical devices -- Part 10: Tests for irritation and skin sensitization.
- **ISO 10993-11:2017/EN ISO 10993-11:2018:** Biological evaluation of medical devices – Part 11: Tests for systemic toxicity
- **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
- **(EN) ISO 10993-23:2021:** Biological evaluation of medical devices – Part 23: Tests for irritation
- **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
- **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) ISO 11737-1:2018, A1:2021:** Sterilization of health care products - Microbiological methods - Part 1: Determination of a population of microorganisms on products
- **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.

9 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.1	24/03/2020	Initial version	
A.2	26/07/2021	Update 2021	
A.3	01/06/2022	MDR conformity assessment round 1	Date: 17/07/2023 Validation language: English
A.4	11/10/2022	Update 2022: addition PMCF data	Not submitted for validation, as there were no significant changes that required validation.
A.5	18/09/2023	Update 2023	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

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.