Summary of Safety and Clinical Performance

FertiCult IVF media

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 IVF medium
FertiCult IVF medium with phenol red
FertiCult IVF medium with gentamicin
FertiCult IVF medium with phenol red and gentamicin

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

5411967FECU1SU

1.5 Medical device nomenclature description/text

Applicable EMDN code: U08020503 - Materials/culture media 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 FertiCult IVF media: 13/12/2018

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

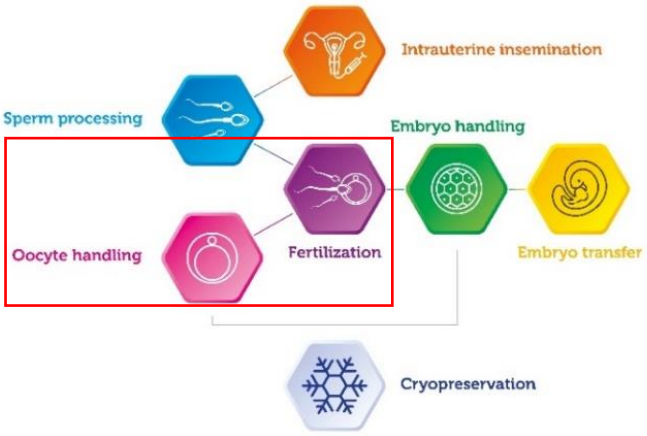
2.1 Intended purpose

FertiCult IVF media are intended for washing and holding of human oocytes, and for performing fertilization by in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) (until 2PN stage).

2.2 Indication(s) and intended patient groups

FertiCult IVF media are used in specialized laboratories performing assisted fertilization technologies, including IVF and ICSI. The intended users are assisted reproductive technologies (ART) professionals (lab technicians, embryologists or medical doctors).

The red square in the figure below shows the steps in the ART process wherein FertiCult IVF media can be used.



Direct physical contact only occurs between the media and human gametes/embryos. There is no contact with the human body as these media are not intended for embryo transfer.

2.3 Contraindications and/or limitations

Not applicable, no contra-indications/ limitations for FertiCult IVF media.

3 Device description

3.1 Description of the device

- For the principle of operation, reference is made to the IFU: FP09 I07 R01.
- FertiCult IVF media are not intended for single use. Multiple single-procedures can be performed. 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 IVF media are sterilized using aseptic processing techniques (filtration).
- FertiCult IVF media are is a bicarbonate-buffered balanced salt solution, supplemented with glucose, lactate, pyruvate, and human serum albumin (HSA). The product is also available with phenol red and/or gentamicin.
  The inclusion of HSA (medicinal substance derived from human blood plasma) in ART media from FertiPro is approved by the European Medicine Agency (EMA).
  The added gentamicin (medicinal substance) complies with Ph. Eur. Monograph Standard 0331, is EDQM-certified and is approved by the Medicines Evaluation Board (MEB, the competent authority of The Netherlands).

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

Not applicable, 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

Not applicable, no accessories identified.

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

Not applicable, no specific material (i.e. not general (ART) labware or media).

4 Risks and warnings

4.1 Residual risks and undesirable effects

The output from the clinical evaluation reports of FertiCult IVF media, gentamicin and HSA are taken into account in the risk assessment report of FertiCult IVF media in order to determine the benefits/ risk ratio.

The only remaining residual risk is the inclusion of HSA in FertiCult IVF media. The inclusion of HSA (which is a medicinal substance derived from human blood plasma) is approved by the EMA.

The major benefit of HSA in FertiCult IVF media is:

- 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

A potential risk associated to the inclusion of HSA is batch-to-batch variation and the transmission of viral or prion-carried diseases:

- Batch-to-batch variation is 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 is routinely performed as part of the batch release of HSA (incoming inspection) and as part of the FertiCult IVF media batch release.
- Transmission of 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 FertiCult IVF media and human gametes or embryos. There is no contact with the human body as these media are not intended for embryo transfer. The instructions for use/MSDS clearly warn that the medium contains human albumin solution and that protective clothing should be worn..

Based on this analysis it is concluded that the benefit of adding HSA to FertiCult IVF media outweighs the risk, and the overall residual risk related to the use of FertiCult IVF media has been judged acceptable.

Furthermore, following information is provided to the customer:

- Product composition is clearly indicated on the labels and IFU
- IFU contains the following warnings:
  - 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.

No other known undesirable side-effects are identified.

4.2 Warnings and precautions

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 discoloured (if medium contains phenol red), 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
- Products that include gentamicin should not be used on a patient that has a known allergy to gentamicin or similar antibiotics
- 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.
- Keep in its original packaging until the day of use.
- Aseptic technique should be used to avoid possible contamination even when the product contains gentamicin.
- 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

Not applicable, no field safety corrective actions with regard to FertiCult IVF media were needed so far.

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

5.1 Real-world evidence analyses

A literature search is performed on a yearly basis, to investigate whether clinical embryology and ART outcomes obtained during the search are consistent with the clinical outcomes described in the following benchmark papers from the European Society of Human Reproduction and Embryology (ESHRE):

- Embryological outcomes:

ESHRE Special Interest Group of Embryology, 'The Vienna consensus: report of an expert meeting on the development of art laboratory performance indicators', Hum Reprod Open, 2017: hox011.	ICSI normal fertilization rate:	≥65% (lower range: 55%)
	IVF normal fertilization rate:	≥60% (lower range: 50%)

- Clinical ART outcomes

	IVF	**ICSI**	**Frozen embryo replacement (FER):**
Smeenk, J., C. Wyns, C. De Geyter, M. Kupka, C. Bergh, I. Cuevas Saiz, D. De Neubourg, K. Rezabek, A. Tandler-Schneider, I. Rugescu, and V. Goossens. 2023. 'ART in Europe, 2019: results generated from European registries by ESHRE', Hum Reprod, 38(12): 2321–2338.	Clinical pregnancy rate per aspiration: **27.0%** *(range: 18.4 – 53.1%)*	Clinical pregnancy rate per aspiration: **24.9%** *(range: 16.0 – 46.1%)*	Pregnancy rate per thawing: **36.5%** *(range: 22.5 – 50.1%)*
	Clinical pregnancy rate per transfer: **38.1%** *(range: 27.4 – 63.0%)*	Clinical pregnancy rate per transfer: **37.2%** *(range: 26.9 – 52.1%)*	Pregnancy rate per transfer: **37.1%** *(range: 22.5 – 56.0%)*
	Delivery rate per aspiration: **19.3%** *(range: 12.3 – 29.4%)*	Delivery rate per aspiration: **17.8%** *(range: 10.6 – 28.6%)*	Delivery rate per thawing: **25.8%** *(range: 7.2 – 41.4%)*
	Delivery rate per transfer: **27.6%** *(range: 17.9 – 45.9%)*	Delivery rate per transfer: **27.0%** *(range: 12.1 – 39.4%)*	Delivery rate per transfer: **26.2%** *(range: 8.4 – 42.4%)*

There were 4 papers retrieved in literature studying the performance of FertiCult IVF media. It can be concluded from these papers that embryological and clinical ART outcomes, when FertiCult IVF media were are consistent with the outcomes described in the benchmark papers.

A reference list to the papers is provided below:

- Boucret, L., L. Tramon, P. Saulnier, V. Ferre-L'Hotellier, P. E. Bouet, and P. May-Panloup. 2021. 'Change in the Strategy of Embryo Selection with Time-Lapse System Implementation-Impact on Clinical Pregnancy Rates', *J Clin Med*, 10.
- Fishel, S., A. Campbell, F. Foad, L. Davies, L. Best, N. Davis, R. Smith, S. Duffy, S. Wheat, S. Montgomery, A. Wachter, and A. Beccles. 2020. 'Evolution of embryo selection for IVF from subjective morphology assessment to objective time-lapse algorithms improves chance of live birth', *Reprod Biomed Online*, 40: 61-70.
- Matorras, R., A. Navarro, D. Ramos, I. Malaina, J. Irazusta, A. Vendrell, A. Fernandez, M. Ferrando, and F. Quintana. 2022. 'Physical activity and sperm quality: influence in sperm donors'*, Reprod Biol Endocrinol*, 20: 83.
- Stukaitė-Ruibienė E, Gudlevičienė Ž, Amšiejienė A, Dagytė E, Gricius R, Grigalionienė K, Utkus A, Ramašauskaitė D. 2022. 'Implementation and Evaluation of Preimplantation Genetic Testing at Vilnius University Hospital Santaros Klinikos.', *Acta Medica Lituanica*, 29: 225-35.

5.2 Device registers

Clinical data was collected from five IVF clinics worldwide (with a total of 5832 cycles). The reported embryological and/or clinical ART outcomes of all IVF clinics using FertiCult IVF media are consistent with the outcomes described in the above mentioned benchmark papers. When IVF clinics compared FertiCult IVF media with a commercial medium with a similar intended use, comparable embryological and ART outcomes were obtained.

5.3 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.

5.4 An overall summary of the clinical performance and safety

FertiCult IVF media functions as stated by the manufacturer: i.e. FertiCult IVF media can be used for washing and holding of human oocytes, and performing fertilization by IVF and ICSI (until 2PN).

This is established by clinical data retrieved from literature and IVF centers which demonstrate that embryological outcomes and pregnancy/delivery rates of procedures in which FertiCult IVF media were used are consistent with the published outcomes as reported by the Vienna consensus group and the ESHRE. In addition, IVF centers reported comparable embryological and ART outcomes when FertiCult IVF media was compared with a commercial medium with a similar intended use.

Furthermore, there is no evidence from clinical data, registered complains, market/customer feedback and/or vigilance that FertiCult IVF media are toxic for gametes and embryos, nor that the media have risk for mutagenity, oncogenicity, teratogenity, carcinogenity, cytotoxicity, allergenicity and irritancy for patients and users.

5.5 Ongoing or planned PMS/PMCF

PMS/PMCF for FertiCult IVF media (including PMS/PMCF for the gentamicin and HSA component included in some variants of FertiCult IVF media) 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 SSCP will be updated with information from the PMS/PMCF, 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 IVF media are available on the European Union or international markets. Besides the media with similar intended use, there are no other alternative treatments that can be used for washing and holding of human oocytes, and performing fertilization by IVF and ICSI (until 2PN).

7 Suggested profile and training for users

FertiCult IVF media are used in specialized laboratories performing fertilization techniques, including IVF and ICSI. The intended users are ART 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 technical standards apply to FertiCult IVF media:

ISO 13485:2016 EN ISO 13485:2016 (Amd 11:2021)	Medical devices — Quality management systems — Requirements for regulatory purposes.
MDR 2017/745	European Medical Device Regulation 2017/745 of 5 April 2017
EN 556-2:2015	Sterilization of medical devices – Requirements for medical devices to be designated 'STERILE' – Requirements for aseptically processed medical devices
(EN) ISO 20417:2021	Information to be supplied by the manufacturer
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
ISO 23640:2011 EN ISO 23640:2015	In vitro diagnostic medical devices: Evaluation of stability of in vitro diagnostic reagents.
(EN) ISO 11737-1:2018, A1:2021	Sterilization of health care products - Microbiological methods - Part 1: Determination of a population of microorganisms on products
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
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
(EN) ISO 14644-3:2019	Cleanrooms and associated controlled environments - Part 3: Test methods
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/A1:2023	Biological evaluation of medical devices – Part 18: Chemical characterization of medical device materials within a risk management process
(EN) ISO 22442-1: 2020	Medical Devices utilizing animal tissues and their derivatives: Part 1: Application of risk management
Ph. Eur. 331	European Pharmacopoeia monograph 331 – Gentamicin sulfate
Ph. Eur. 0255	European Pharmacopoeia monograph 0255 – Human albumin solution

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

Not applicable, since FertiCult IVF media are for professional use only.

10 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.4	19/04/2021	Initial validated version	Version A.4 is validated by the Notified Body Validation language: English
A.5	19/04/2022	Update 2022: addition PMCF data	Not submitted for validation, as there were no significant changes that required validation.
A.6	10/05/2023	Update 2023: addition PMCF data	Not submitted for validation, as there were no significant changes that required validation.
A.7	02/05/2024	Update 2024: addition PMCF data	Not submitted for validation, as there were no significant changes that required validation.