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).

The media should be pre-equilibrated in a CO_2 incubator and are mainly used for holding the oocytes/early embryo in the CO_2 incubator.
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.

2.2 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 IVF professionals (lab technicians, embryologists or medical doctors).

2.3 Contraindications and/or limitations

There are no reasonably foreseeable medical conditions for which FertiCult IVF media are not to be used.

3 Device description

3.1 Description of the device

FertiCult IVF media are ready-to-use media for washing and holding human oocytes and for performing fertilization by IVF or ICSI (until 2PN). The media are not intended to be used for embryo transfer. The media are complete and need no further additives. They consist of a balanced salt solution supplemented with human serum albumin (HSA) and carbohydrate energy sources such as glucose (at high concentration), pyruvate and lactate.

The inclusion of HSA (which is a medicinal substance derived from human blood plasma) in ART media from FertiPro is approved by the EMA (European Medicine Agency).

FertiCult IVF media are also available with phenol red and/or gentamicin. The added gentamicin complies with Ph. Eur. Monograph Standard 0331, is EDQM-certified and is approved by the MEB (Medicines Evaluation Board, the competent authority of The Netherlands).

The devices are not intended for single use. Multiple single-procedures can be performed with one bottle of FertiCult IVF media. 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).

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

There are no accessories for FertiCult IVF media.

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 only remaining residual risk is the inclusion of HSA in FertiCult IVF media. 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, Mouse Embryo Assays 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**.
  - ↔ Human albumin solution 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.

The major benefit of HSA in FertiCult IVF media 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 this 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 FertiCult IVF media with inclusion of HSA has been judged acceptable.

With respect to the above, 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 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

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 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

No field safety corrective actions with regard to FertiCult IVF media were needed.

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

5.1 Benchmark data

- Embryological outcomes:

Embryology outcomes when FertiCult IVF media are used should be consistent with the competency limits as reported by the ESHRE Vienna consensus group (ESHRE Special Interest Group of Embryology 2017):

Competency limits reported by the ESHRE Special Interest Group of Embryology and Alpha Scientist in Reproductive Medicine in 2017. *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

Clinical ART outcomes (pregnancy and delivery rates) when FertiCult IVF media are used should be consistent with the ART outcomes described in the benchmark paper from the ESHRE (European Society of Human Reproduction and Embryology). The ESHRE publishes each year 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 is summarized in the table below:

	In vitro fertilization (IVF):	**Intra cytoplasmic sperm injection (ICSI):**	**Frozen embryo replacement (FER):**	**Intrauterine insemination(IUI):**
ART in Europe, 2018: results generated from European registries by ESHRE *C. Wyns et al., ART in Europe, 2018: results generated from European registries by ESHRE. Hum Reprod Open. 2022; doi: 10.1093/hropen/hoac022*	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%)*	**using husband semen (IUI-H):** Delivery rate per cycle: **9.5%** *(range: 3.3 – 31.6%)* **using donor semen (IUI-D):** Delivery rate per cycle: **14.9%** *(range: 3.2 – 31.4%)*

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 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 are used, fall within the range of the outcomes described in the benchmark papers, suggesting a safe and adequate performance of FertiCult IVF media.

5.3 Device registers

In cooperation with an IVF clinic in Europe, two trials were set up in which FertiCult IVF media were compared with a commercial standard IVF medium. From these trials it could be concluded that FertiCult IVF media are safe and effective media for washing/handling of oocytes and for fertilization. Indeed, comparable embryological and clinical outcomes were reported when oocytes were washed/handled and/or fertilized with FertiCult IVF media versus a commercial standard IVF medium. In addition, embryological outcomes, as well as pregnancy and delivery rates of procedures in which FertiCult IVF media were used were consistent with the published outcomes as reported by the benchmark papers.

Also, data from three other IVF clinics in Europe demonstrated highly comparable fertilization and blastocyst rates when using FertiCult IVF medium for fertilisation by ICSI or the control medium from a competitor. The embryology outcomes reported by the these clinics as well as pregnancy and delivery rates of procedures in which FertiCult IVF media were used were consistent with the published outcomes as reported by the benchmark papers, indicating that FertiCult IVF media not interfere with the general ART procedure.

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.

5.5 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 pregnancy and delivery rates of IVF and ICSI procedures in which FertiCult IVF media are used are consistent with the published outcomes as reported by the ESHRE, or are consistent with the minimal competency limits reported by the Vienna consensus group when it concerns embryological outcomes. In addition, the IVF centers reported comparable embryological and/or clinical ART outcomes when oocytes were washed/handled and/or fertilized with FertiCult IVF media versus 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.

5.6 Ongoing or planned post-market clinical follow-up

Post-market clinical follow-up for FertiCult IVF media (including PMCF for the HSA and gentamicin component included in (some variants of) FertiCult IVF media) will be performed at least yearly.

This Summary of Safety and Clinical Performance will be updated with information from the post-market clinical follow-up, 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 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 IVF media:

- **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.
- **EN ISO 23640:2015 / ISO 23640:2011**: 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 in line with the EU list of harmonized standards drafted in support of Council Directive 93/42/EEC and MDR 2017/745)

- **ISO 10993-1:2018 / EN ISO 10993-2020**: 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 13485:2016 / EN ISO13485:2016 (Amd 11:2021)**: Medical devices – Quality management systems – Requirements for regulatory purposes
- **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 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
- **NBOG BPG 2014-3**: Guidance for manufacturers and Notified Bodies on reporting of Design Changes and Changes of the Quality System
- **IEC 62366-1:2015 (Amd 1:2020)**: Medical devices - Part 1: Application of usability engineering to medical devices
- **(EN) ISO 22442-1: 2020**: Medical Devices utilizing animal tissues and their derivatives: Part 1: Application of risk management
- **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

9 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.1	04/02/2020	Initial version	Date: not yet Validation language: English
A.2	29/09/2020	MDR conformity assessment (1)	Date: not yet Validation language: English
A.3	10/12/2020	MDR conformity assessment (2)	Date: not yet Validation language: English
A.4	19/04/2021	MDR conformity assessment (3) + Update 2021	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.

10 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.