Summary of Safety and Clinical Performance FertiVit™ Cooling/ FertiVit™ Warming

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)
FertiVit™ Cooling/ FertiVit™ Warming

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
5411967FVCW1WR

1.5 Medical device nomenclature description/text
Applicable EMDN code:
U08020501: Materials/solutions for freezing/thawing for assisted reproduction

1.6 Class of device
Class III device according to Annex VIII of the MDR

1.7 Year when the first certificate (CE) was issued covering the device
2016

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
FertiVit™ Cooling/ FertiVit™ Warming are a set of media for vitrification and warming of human oocytes and embryos (zygote till blastocyst).

2.2 Indication(s) and intended patient groups
FertiVit™ Cooling/ FertiVit™ Warming is used to store oocytes or embryos before assisted reproduction treatments (either in vitro fertilization (IVF), intracytoplasmatic sperm injection (ICSI) or embryo transfer). FertiVit™ Cooling/ FertiVit™ Warming is used in specialized laboratories performing fertilization techniques. The intended users are IVF professionals (lab technicians, embryologists, or medical doctors).

The red square in the figure below shows the steps in the assisted reproductive technologies (ART) process wherein FertiVit™ Cooling/ FertiVit™ Warming can be used.

Direct physical contact only occurs between FertiVit™ Cooling/ FertiVit™ Warming and human oocytes/embryos. The device does not come into contact with the human body.

2.3 Contraindications and/or limitations

Not applicable, no contra-indications/ limitations for FertiVit™ Cooling/ FertiVit™ Warming.

3 Device description

3.1 Description of the device

- For the principle of operation, reference is made to the IFU: FP09 I46 03 R01.
- FertiVit™ Cooling/ FertiVit™ Warming is not intended for single use. Multiple single-procedures can be performed with one FertiVit™ Cooling/ FertiVit™ Warming kit. 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).
- FertiVit™ Cooling/ FertiVit™ Warming is sterilized using aseptic processing techniques (filtration).
- FertiVit™ Cooling/ FertiVit™ Warming are dimethylsulphoxide (DMSO) /ethylene glycol (EG) based vitrification media (with concentration ranging from 0-20%) that also contain HTF-HEPES, sucrose, ficoll and human serum albumin (HSA).
  The inclusion of HSA (which is a medicinal substance derived from human blood plasma) in ART media from FertiPro is approved by the European Medicine Agency (EMA).

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 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

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

- Vitrification device, preferably closed device
- Freezing tank with liquid nitrogen

4 Risks and warnings

4.1 Residual risks and undesirable effects

The output from the clinical evaluation reports of FertiVit™ Cooling/ FertiVit™ Warming and HSA are taken into account in the risk assessment report of FertiVit™ Cooling/ FertiVit™ Warming in order to determine the benefits / risk ratio.

The only remaining residual risk is the inclusion of HSA in FertiVit™ Cooling/ FertiVit™ Warming. 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 FertiVit™ Cooling/ FertiVit™ Warming is:

- Stabilization of the cell membrane of the oocyte/embryo in the medium
- Carrier and source of essential molecules needed by the oocyte/embryo
- Detoxification by binding waste products from cell metabolism.
- Facilitating oocyte/embryo manipulation by preventing adsorption to the surface through saturation of potential binding sites.
- Prevention of physical damage during cryopreservation

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 FertiVit™ Cooling/ FertiVit™ Warming 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. The use of FertiVit™ Cooling/ FertiVit™ Warming is restricted to the vitrification and warming of human oocytes and embryos and is not intended to be in direct contact with users or patients. Even so, the IFU/ material safety data sheet clearly warn that FertiVit™ Cooling/ FertiVit™ Warming 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 FertiVit™ Cooling/ FertiVit™ Warming outweighs the risk, and the overall residual risk related to the use of FertiVit™ Cooling/ FertiVit™ Warming 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 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
- Aseptic technique should be used to avoid possible contamination.
- 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 FertiVit™ Cooling/ FertiVit™ Warming were needed so far.

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

5.1 Real-world evidence analyses

A literature search is performed, to investigate whether clinical data obtained with FertiVit™ Cooling/ FertiVit™ Warming are consistent with the embryological competency limits and/or with the clinical ART outcomes as described in benchmark papers (see tables below).

- Regarding embryo cryosurvival rate, the following competency limits are reported :

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	Embryo cryosurvival rate:	≥90%

- Regarding oocyte cryosurvival rate and embryo morphological survival rate, the following competency limits are reported :

Alpha Scientists In Reproductive Medicine, 2012. 2012. **'The Alpha consensus meeting on cryopreservation key performance indicators and benchmarks: proceedings of an expert meeting'**, Reprod Biomed Online, 25: 146-67.	Oocyte KPI values: Oocyte survival rate: ≥70%
	Zygote KPI values: Morphological survival rate: ≥70%
	Embryo KPI values: - Morphological survival rate (fully intact): ≥70% - Morphological survival rate (≥ 50% intact): ≥85%

- Regarding ART outcomes, the following rates are reported:

Most recent report: Smeenk, J., C. Wyns, C. De Geyter, M. Kupka, C. Bergh, I. Cuevas Saiz, D. De Neubourg, K.	**In vitro fertilization (IVF)*:** Clinical pregnancy rate per aspiration: **27.0%**	**Intra cytoplasmic sperm injection (ICSI)*:** Clinical pregnancy rate per aspiration: **24.9%**	**Frozen embryo transfer (FET):** Pregnancy rate per thawing: **36.5%**	**Frozen oocyte replacement (FOR)**:**

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.	*(range: 18.4 – 53.1%)* Clinical pregnancy rate per transfer: **38.1%** *(range: 27.4 – 63.0%)* Delivery rate per aspiration: **19.3%** *(range: 23.3 – 29.4%)* Delivery rate per transfer: **27.6%** *(range: 17.9 – 45.9%)*	*(range: 16.0 – 46.1%)* Clinical pregnancy rate per transfer: **37.2%** *(range: 26.9 – 52.1%)* Delivery rate per aspiration: **17.8%** *(range: 10.6 – 28.6%)* Delivery rate per transfer: **27.0%** *(range: 12.1 – 39.4%)*	*(range: 22.5 – 50.1%)* Pregnancy rate per transfer: **37.1%** *(range: 22.5 – 56.0%)* Delivery rate per thawing: **25.8%** *(range: 7.2 – 41.4%)* Delivery rate per transfer: **26.2%** *(range: 8.4 – 42.4%)*	Pregnancy rate per transfer: **29.5%** Delivery rate per transfer: **24.4%**

*Values generally without freezing of oocyte/embryo
** ART outcome for FOR is represented in the ESHRE article, not in the supplementary data. No range for FOR is reported.

One article was retrieved in literature that indicate a safe and adequate performance of FertiVit™ Cooling/ FertiVit™ Warming for oocyte and embryo vitrification. Overall, it can be concluded from this paper that embryological and clinical ART outcomes, when FertiVit™ Cooling/ FertiVit™ Warming was used, are consistent with the outcomes described in the benchmark papers.

A reference list to the papers is provided below:

- *Papatheodorou, A., P. Vanderzwalmen, Y. Panagiotidis, S. Petousis, G. Gullo, E. Kasapi, M. Goudakou, N. Prapas, K. Zikopoulos, I. Georgiou, and Y. Prapas. 2016. 'How does closed system vitrification of human oocytes affect the clinical outcome? A prospective, observational, cohort, noninferiority trial in an oocyte donation program', Fertil Steril, 106: 1348-55.*

5.2 Device registries

Number of cycles with the use of FertiVit™ Cooling/ FertiVit™ Warming collected from IVF clinics are summarized in the table below:

IVF center	Vitrification device used	Oocytes: number of cycles	Embryos: number of cycles
Iakentro Institute (Greece)	Closed device (VitriSafe and HSV)	See article: Papatheodorou et al.	1192
IVF center (Austria)	Closed device (VitriSafe)	129	3868
IVF center (Belgium)	Closed device (VitriSafe)	-	553
IVF center (Europe)	Closed device (HSV)	32	137
IVF center (Europe)	Open device*	18	329
IVF center (Europe)	Open device*	-	21 (note that only FertiVit Warming was used)
IVF center (Europe)	Open device*	21	290
IVF center (Greece)	Closed device (VitriSafe and HSV)	26	62

* Note that FertiPro recommends the use of closed vitrification devices

The reported embryological and/or clinical ART outcomes of all IVF clinics using FertiVit™ Cooling/ FertiVit™ Warming are consistent with the outcomes described in the benchmark papers. These results indicate that FertiVit™ Cooling/ FertiVit™ Warming is safe and effective for the vitrification of oocytes and embryos.

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 PMS/ PMCF analysis.

5.4 An overall summary of the clinical performance and safety

FertiVit™ Cooling/ FertiVit™ Warming functions as stated by the manufacturer: i.e. vitrification and warming of human oocytes and embryos (zygote till blastocyst)[1].

This is established by clinical data which demonstrate that embryology and/or clinical ART outcomes of procedures in which FertiVit™ Cooling/ FertiVit™ Warming is used for oocyte/embryo vitrification are consistent with the published outcomes as reported by the ESHRE (most recent report (Smeenk et al. 2023)), and/or that the oocyte or embryo survival rate of oocytes/embryos vitrified/warmed with FertiVit™ Cooling/ FertiVit™ Warming is higher than the minimal competency limit published by the Alpha Scientists in Reproductive Medicine (Alpha Scientists In Reproductive Medicine 2012) or reported by the Vienna consensus group (ESHRE Special Interest Group of Embryology 2017) for oocytes and embryos respectively.

Moreover, there is no evidence from the clinical data, as well as from the registered complains, market/customer feedback and/or vigilance that FertiVit™ Cooling/ FertiVit™ Warming is (geno-)toxic for oocytes and/or embryos and causes DNA damage, nor that the medium has a risk for mutagenity, oncogenicity, teratogenity, carcinogenity, cytotoxicity, allergenicity and irritancy for patients and users.

5.5 Ongoing or planned PMS/ PMCF

PMS/ PMCF for FertiVit™ Cooling/ FertiVit™ Warming (including PMS/ PMCF for the HSA component included in FertiVit™ Cooling/ FertiVit™ Warming) 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

Cryopreservation of embryos at different stages and cryopreservation of oocytes is a necessary tool in ART, to help couples that require fertility treatment. Cryopreservation can be obtained by using slow freezing or vitrification for which FertiVit™ Cooling/ FertiVit™ Warming is designed. Based on peer-reviewed scientific literature, it can be concluded that vitrification is better and safer option for cryopreservation when compared to slow freezing. Devices with similar intended use as FertiVit™ Cooling/ FertiVit™ Warming are available on the European Union or international markets.

7 Suggested profile and training for users

FertiVit™ Cooling/ FertiVit™ Warming is 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)

The following technical standards apply to FertiVit™ Cooling/ FertiVit™ Warming:

MDR 2017/745	European Medical Device Regulation 2017/745 of 5 April 2017.
(EN) ISO 13485:2016/EN ISO13485:2016/Ac:2018	Medical devices — Quality management systems — Requirements for regulatory purposes.
(EN) ISO 20417:2021	Medical devices: information supplied by the manufacturer.
ISO 10993-1:2018/EN ISO 10993-1:2020:	Biological evaluation of medical devices -- Part 1: Evaluation and testing.

[1] Note that no data is available on the clinical use of FertiVit for vitrification of zygotes and cleavage stage embryos. Therefore, clinical safety and performance of FertiVit for these intended uses was based on equivalence to respectively:

- The in-house medium used in: *Vanderzwalmen, P., N. H. Zech, F. Ectors, A. Stecher, B. Lejeune, S. Vanderzwalmen, and B. Wirleitner. 2012. 'Blastocyst transfer after aseptic vitrification of zygotes: an approach to overcome an impaired uterine environment', Reprod Biomed Online, 25: 591-9.*
- *VitriFreeze ES (FertiPro NV): Kaartinen, N., K. Kananen, H. Huhtala, S. Keränen, H. Tinkanen. 2016. 'The freezing method of cleavage stage embryos has no impact on the weight of the newborns', J Assist Reprod Genet, 33(3): 393–399.*
- *VitriFreeze ES (FertiPro NV): Hallamaa, M., J. Seikkula, S. Willman, H. Ollila, and V. Jokimaa. 2021. 'Pregnancy potential and perinatal outcomes of embryos cryopreserved twice: a case-control study', RBMO, 43.*

(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
(EN) ISO 14971:2019	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 (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)
ISO 11737-1:2018, A1:2021 / EN ISO 11737-1:2018	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
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.
Ph. Eur. 0255	European Pharmacopoeia monograph 0255 – Human albumin solution

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

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

10 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.4	20/12/2021	Initial validated version	Version A.4 is validated by the Notified Body Validation language: English
A.5	21/04/2022	Update 2022	Not submitted for validation, as there were no significant changes that required validation.
A.6	28/04/2023	Update 2023	Not submitted for validation, as there were no significant changes that required validation.
A.7	28/03/2024	Update 2024	Not submitted for validation, as there were no significant changes that required validation.