Summary of Safety and Clinical Performance

FertiVit Cooling / 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 / Warming kit

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/Warming is a set of media for vitrification and warming of human oocytes and embryos (zygote till blastocyst).

2.2 Indication(s) and intended patient groups

Cryopreservation of embryos at different stages and cryopreservation of oocytes is of crucial and increasing importance in assisted reproductive medicine, to help couples that require fertility treatment.

- Nowadays fertility preservation is in the main focus of oocyte freezing, including all clinical situations with emerging loss of the ovarian reserve, e. g. cancer treatment, ovarian surgeries, or premature ovarian failure (POF)
- Additionally situations where women decide to delay childbearing with the risk of a decrease in oocyte quality due to advanced female age require fertility preservation.
- Embryo cryopreservation has decreased the number of fresh embryos transferred and makes it possible to cancel embryo transfer in case any obstacle before embryo transfer occurs (like ovarian hyper-stimulation syndrome, no optimal endometrial thickness, bleeding etc.).
- In certain countries where the law prohibits embryo cryopreservation and gamete donation, excess oocytes have been cryopreserved for future use.
- In order to avoid the accumulation of too many embryos in containers, oocyte vitrification is an option.
- For logistic reasons when the man cannot product the semen sample or when the man is absent.

Direct physical contact only occurs between the media products and human oocytes/embryos. The products do not come into contact with the human body.

2.3 Contraindications and/or limitations

There are no contra-indications for using FertiVit Cooling/Warming of FertiPro NV for the vitrification and warming of human oocytes and/or embryos between zygote and blastocyst stage.

3 Device description

3.1 Description of the device

FertiVit Cooling / Warming is a set of ready-to-use media for vitrification and warming of human oocytes and embryos.

Vitrification is the process of cryopreservation using high initial concentrations of cryoprotectant and ultra-rapid cooling to solidify the cell into a glass-like state without the formation of ice. FertiVit Cooling / 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 Assisted Reproductive Technology (ART) media from FertiPro is approved by the European Medicine Agency (EMA).

The device is not intended for single use. Multiple single-procedures can be performed with one FertiVit Cooling/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/Warming 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 FertiVit Cooling/Warming are identified.

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

FertiVit Cooling/Warming is intended to be used with the following devices:

- Vitrification device (preferably closed device e.g. High Security Straws (Cryo Bio Systems) or VitriSafe (Nextclinic)).
- Freezing tank with liquid nitrogen

4 Risks and warnings

4.1 Residual risks and undesirable effects

The only remaining residual risk is the inclusion of HSA in FertiVit Cooling/Warming. 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 is routinely performed as part of the batch release criteria of HSA (incoming inspection) and as part of the FertiVit Cooling/ Warming 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. The use of FertiVit Cooling/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 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 FertiVit Cooling / Warming is clear:

- 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

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 FertiVit Cooling/Warming for vitrification and warming of human oocytes and embryos 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 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. FertiVit Cooling/Warming does not contain any antibiotics.
- 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 FertiVit Cooling/Warming 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 data (pregnancy and delivery rates) obtained during the search are consistent with the embryological competency limits and/or with the clinical ART outcomes described in benchmark papers (see tables below).

- **Clinical data** obtained from IVF centers should be consistent with the clinical outcomes described in the benchmark paper from the ESHRE (most recent report (Wyns et al. 2022)):

ART in Europe, 2018: results generated from European registries by ESHRE A total of 1 007 598 treatment cycles, involving 162 837 with IVF, 400 375 with ICSI, 309 475 with frozen embryo transfer (FET), 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.	**In vitro fertilization (IVF)*:** 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%)*	**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%)*	**Frozen embryo transfer (FET):** 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%)*	**Frozen oocyte replacement (FOR)**:** Pregnancy rate per transfer: **29.5%** Delivery rate per transfer: **21.7%**

*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.

- **The embryo cryosurvival rate** must be higher than the minimal competency limit as reported by the ESHRE Vienna consensus group in 2017 (ESHRE Special Interest Group of Embryology 2017):

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)	Embryo cryosurvival rate:	≥90%

- **The oocyte cryosurvival rate and embryo morphological survival rate** must be higher than the minimal competency limit as reported by the Alpha Scientists in Reproductive Medicine in 2012 (Alpha Scientists In Reproductive Medicine 2012):

Minimal competency limits reported by the Alpha Scientists in 2012. The Alpha consensus meeting on cryopreservation key performance indicators and benchmarks: proceedings of an expert meeting (Alpha Scientists In Reproductive Medicine 2012)	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%)

One article was retrieved that indicates the safe and adequate performance of FertiVit Cooling/Warming for oocyte vitrification. The oocyte survival rate as reported in the paper is consistent with the minimal competency limit as reported by the Alpha Scientists in Reproductive Medicine in 2012 (Alpha Scientists In Reproductive Medicine 2012). The pregnancy/delivery rates per transfer as reported in the article are consistent with the ESHRE reference value for FOR (Wyns et al. 2021):

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/Warming collected from IVF clinics are summarized in the table below:

IVF center	Vitfrification device used	Oocytes: number of cycles	Embryos: number of cycles
Iakentro Institute (Greece)	Closed device, VitriSafe (Nextclinic) and HSV (CBS)	See 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 (CBS)	32	137
IVF center (Europe)	Open device*	18	385
IVF center (Europe)	Open device*	-	21 (note that only FertiVit Warming was used)
IVF center (Europe)	Open device*	21	290

* Note that FertiPro recommends the use of closed vitrification devices

The reported pregnancy/delivery rates of all IVF clinics using FertiVit Cooling/Warming are consistent with the ESHRE reference values for FOR/FET (most recent report (Wyns et al. 2022)). Also, all reported oocyte or embryo cryosurvival rates are higher than the minimal competency limit published by the Alpha Scientists in Reproductive Medicine (Alpha Scientists In Reproductive Medicine 2012) or by the ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine (ESHRE Special Interest Group of Embryology 2017). These results indicate that FertiVit Cooling/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 PMCF analysis.

5.4 An overall summary of the clinical performance and safety

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

This is established by clinical data which demonstrate that embryology and/or clinical ART outcomes of procedures in which FertiVit Cooling/Warming is used for oocyte/embryo vitrification are consistent with the published outcomes as reported by the ESHRE (most recent report (Wyns et al. 2022)), and/or that the oocyte or embryo survival rate of oocytes/embryos vitrified/warmed with FertiVit Cooling/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.

[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.*

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/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. These data further suggest that the benefit risk ratio of FertiVit Cooling/Warming remains acceptable.

5.5 Ongoing or planned post-market clinical follow-up

Post-market clinical follow-up for FertiVit Cooling/Warming (including PMCF for the HSA component included in FertiVit Cooling/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.

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

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 the slow-cooling method or the vitrification technique for which FertiVit Cooling/warming is designed. Based on scientific literature, it is concluded that vitrification is a similar or even better and safer option for cryopreservation when compared to slow freezing. Devices with similar intended use as FertiVit Cooling/Warming are available on the European Union or international markets.

The procedure for successful cryopreservation by vitrification of embryos has been the subject of intense research over many years. Cryopreservation of oocytes is a more recent technique but has been extensively studied in the last years. As indicated in the guideline from the Practice Committees of the ASRM (American Society for Reproductive Medicine) and SART (Society for Assisted Reproductive Technology), the technique of vitrifying oocytes should no longer be considered as an experimental procedure[2].

7 Suggested profile and training for users

FertiVit Cooling / Warming is used in specialized laboratories performing fertilization techniques, such as IVF and Intra Cytoplasmic Sperm Injection (ICSI). The intended users are ART professionals (including 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 FertiVit Cooling/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

[2] Reference is made to the following guideline: The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology: Mature oocytes cryopreservation: a guideline. Fertil Steril 2013(99):37-43.

- **ISO 10993-1:2018/EN ISO 10993-1:2020**: Biological evaluation of medical devices -- Part 1: Evaluation and testing.
- **(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.
- **ISO 13408-6:2005 (Amd 1:2013)/EN ISO 13408-6:2011**: Aseptic processing of health care products – Part 6: Isolator systems.
- **ISO 14644-1:2015/EN ISO 14644-1:2016**: 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.
- **ISO 15223-1: 2021/(EN) ISO 15223-1:2016**: 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.

9 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.

10 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.1	07/05/2021	Initial version	Date: not yet Validation language: English
A.2	15/10/2021	BSI review round 1	Date: not yet Validation language: English
A.3	29/10/2021	BSI review round 2	Date: not yet Validation language: English

A.4	20/12/2021	BSI review round 3	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.

11 References

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.

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, S. Vidakovic, and V. Goossens. 2021. 'ART in Europe, 2017: results generated from European registries by ESHRE', *Hum Reprod Open*, 2021: hoab026.