SUMMARY OF SAFETY AND CLINICAL PERFORMANCE

VITRIFREEZE™ (ES)/ VITRITHAW™ (ES)

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)

VitriFreeze™/ VitriThaw™
VitriFreeze™ ES/ VitriThaw™ ES

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

5411967VITRI149

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 (Regulation (EU) 2017/745)

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

- CE marking according to the Council Directive 93/42/EEC:
  - VitriFreeze/VitriThaw: 2005
  - VitriFreeze ES/VitriThaw ES: 2009
- CE marking according to Regulation (EU) 2017/745 (MDR): 22/06/2022

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

VitriFreeze™/ VitriThaw™ are a set of media for vitrification and thawing of human embryos (morula till expanded blastocyst stage).

VitriFreeze ES™/ VitriThaw ES™ are a set of media for vitrification and thawing of human embryos (zygote till expanded blastocyst stage).

2.2 Indication(s) and intended patient groups

- **Indications for use:** For use during assisted reproductive technologies (ART) procedures of patients and couples undergoing infertility treatments.

- **Intended users:** The intended users are ART professionals (lab technicians, embryologists, or medical doctors).

- **Intended patient populations:** The target patient population consists of patients and couples undergoing infertility treatments.

2.3 Contraindications and/or limitations

There are no known contra-indications and/or limitations for VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™.

3 Device description

3.1 Description of the device

- For the principle of operation, reference is made to the IFUs: FP09 I46 R01 for VitriFreeze™/ VitriThaw™ and FP09 I46 02 R01 for VitriFreeze ES™/ VitriThaw ES™.
- VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ are not intended for single use. Multiple single-procedures can be performed with one VitriFreeze™/ VitriThaw™ or VitriFreeze ES™/ VitriThaw ES™ 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).
- VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ are sterilized using aseptic processing techniques (filtration).
- VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ are dimethylsulphoxide (DMSO)/ ethylene glycol (EG) based vitrification media (with concentration ranging from 0-20%) that also contain PBS, 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).
- Direct physical contact only occurs between VitriFreeze™/ VitriThaw™ / VitriFreeze ES™/ VitriThaw ES™ and human embryos. The media do not come into contact with the human body.

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 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 system
- Freezing tank with liquid nitrogen

4 Risks and warnings

4.1 Residual risks and undesirable effects

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

The only remaining residual risk is the inclusion of HSA in VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™. The inclusion this medicinal substance derived from human blood plasma in the devices is approved by the EMA.

The benefits of HSA in VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ are:

- 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. 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 VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ 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 VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™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 VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ 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 VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ outweighs the risk, and the overall residual risk related to the use of VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™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 IFU):

- 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. VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ 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 VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ 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 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:

- Embryology SOTA outcomes:

Embryology parameter	Accepted SOTA outcome
Zygote parameters	
Morphological survival rate:	≥ 60%
Cleavage rate (calculated as $\frac{no.\ of\ cleaved\ embryos\ Day\ 2}{no.\ \frac{2PN}{2PB} oocytes\ on\ Day\ 1}$ x 100):	≥85%
Day 2 embryo development rate (calculated as $\frac{no.\ 4-cell\ embryo\ on\ Day\ 2}{no.\ normally\ fertilized\ oocytes}$ x 100):	≥40%
Day 3 embryo development rate (calculated as $\frac{no.\ 8-cell\ embryo\ on\ Day\ 3}{no.\ normally\ fertilized\ oocytes}$ x 100):	≥35%
Implantation rate cleavage stage (calculated as $\frac{no.\ sacs\ seen\ on\ ultrasound}{no.\ embryos\ transferred}$ x 100):	≥15%
Embryo parameters	
Morphological survival rate (fully intact):	≥60%
Morphological survival rate (≥ 50% intact):	≥75%
Day 3 embryo development rate (calculated as $\frac{no.\ 8-cell\ embryo\ on\ Day\ 3}{no.\ normally\ fertilized\ oocytes}$ x 100):	≥35%
Implantation rate cleavage stage (calculated as $\frac{no.\ sacs\ seen\ on\ ultrasound}{no.\ embryos\ transferred}$ x 100):	≥15%
Blastocyst parameters	
Survival rate:	≥80%

Implantation rate cleavage stage (calculated as $\frac{no.\ sacs\ seen\ on\ ultrasound}{no.\ blastocysts\ transferred}$ x 100):	≥25%

- ART SOTA outcomes:

ART parameter	Accepted SOTA outcome
Frozen embryo transfer (FET)	
Pregnancy rate per thawing	22.5 – 50.1%
Pregnancy rate per transfer	22.5 – 56.0%
Delivery rate per thawing	7.2 – 41.4%
Delivery rate per transfer	8.4 – 42.4%

There were 11 articles retrieved in literature studying the performance of VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™. Overall, it can be concluded from these papers that embryological and clinical ART outcomes, when VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ were used, are consistent with the SOTA outcomes.

A reference list to the papers is provided below[1]:

- Jelinkova, L., N. Ditzel, N. Reeka, F. Gagsteiger, M. Moosova, J. Pavelkova, and K. Rezabek. 2006. "The removal of ZP from blastocysts before vitrification increased their survival and also their implantation rates." In *Abstracts of the 22nd Annual Meeting of the ESHRE*. Praque, Czech Republic.
- Shebl, O., T. Ebner, M. Sommergruber, A. Sir, and G. Tews. 2009. 'Cryopreserved blastocysts have a lower implantation but an equal live birth rate as compared to fresh blastocysts of the same quality - a case-control study', *Acta Obstet Gynecol Scand*, 88: 944-7.
- Ebner, T., P. Vanderzwalmen, O. Shebl, W. Urdl, M. Moser, N. H. Zech, and G. Tews. 2009. 'Morphology of vitrified/warmed day-5 embryos predicts rates of implantation, pregnancy and live birth', *Reprod Biomed Online*, 19: 72-8.
- Hallamaa, M., Seikkula, J., Willman, S., Ollila, H., & Jokimaa, V. (2021). Pregnancy potential and perinatal outcomes of embryos cryopreserved twice: a case–control study. *Reproductive BioMedicine Online*, *43*(4), 607-613.
- Debrock, S., K. Peeraer, C. Spiessens, D. Willemen, P. De Loecker, and T. M. D'Hooghe. 2011. 'The effect of modified quarter laser-assisted zona thinning on the implantation rate per embryo in frozen/vitrified-thawed/warmed embryo transfer cycles: a prospective randomized controlled trial', *Hum Reprod*, 26: 1997-2007.
- Chatzimeletiou, K., E. E. Morrison, Y. Panagiotidis, P. Vanderzwalmen, N. Prapas, Y. Prapas, B. C. Tarlatzis, and A. H. Handyside. 2012. 'Cytoskeletal analysis of human blastocysts by confocal laser scanning microscopy following vitrification', *Hum Reprod*, 27: 106-13.
- Kaartinen, N., K. Kananen, H. Huhtala, S. Keranen, and H. Tinkanen. 2016. 'The freezing method of cleavage stage embryos has no impact on the weight of the newborns', *J Assist Reprod Genet*, 33: 393-99.
- Wirleitner, B., M. Schuff, A. Stecher, M. Murtinger, and P. Vanderzwalmen. 2016. 'Pregnancy and birth outcomes following fresh or vitrified embryo transfer according to blastocyst morphology and expansion stage, and culturing strategy for delayed development', *Hum Reprod*, 31: 1685-95

5.2 Device registries

Number of cycles with the use of VitriFreeze™/VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ collected from IVF clinics are summarized in the table below:

IVF center	Number of cycles
IVF center (Europe)	1472
IVF center (Europe)	358
IVF center (Europe)	267
IVF center (Southern Africa)	856

The reported embryological and/or clinical ART outcomes of all IVF clinics using VitriFreeze™/ VitriThaw™ and/or VitriFreeze ES™/ VitriThaw ES™ are consistent with the SOTA outcomes.

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.

[1] 3 additional articles were retrieved that described the safety and performance of the devices. Due to reasons of confidentiality, these papers are not listed in the table. Note however that all outcomes described in these additional articles are consistent with the outcomes as described in the benchmark papers.

5.4 An overall summary of the clinical performance and safety

VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ function as stated by the manufacturer[2]. This is established by clinical data obtained during literature screening and from IVF centers which show that embryological and ART-outcomes of procedures in which VitriFreeze™/VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ are used are consistent with the published SOTA outcomes as reported by the Vienna consensus group, Alpha Scientists in Reproductive Medicine and the ESHRE.

Moreover, there is no evidence from the clinical data, as well as from the registered complains, market/customer feedback and/or vigilance that VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ is (geno-)toxic for embryos and causes DNA damage, nor that the media have a risk for mutagenity, oncogenicity, teratogenity, carcinogenity, cytotoxicity, allergenicity and irritancy for patients and users. No infrequent complications or problems were detected.

5.5 Ongoing or planned PMS/PMCF

PMS/ PMCF for VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ (including PMS/ PMCF for the HSA component included in VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™) 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 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 is a necessary tool in ART, to help couples that require fertility treatment. Cryopreservation can be obtained by using the slow-cooling method or vitrification for which VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™are designed. Based on peer-reviewed scientific literature, it is concluded that vitrification is a better and safer option for cryopreservation when compared to slow freezing.
Devices with similar intended use as VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™are available on the European Union or international markets.

7 Suggested profile and training for users

VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™ are used by 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 VitriFreeze™/ VitriThaw™ and VitriFreeze ES™/ VitriThaw ES™:

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 556-2:2024	Sterilization of medical devices – Requirements for medical devices to be designated 'STERILE' –Requirements for aseptically processed medical devices.
(EN) ISO 20417:2021	Medical devices: information supplied by the manufacturer.
(EN) 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 17665-1:2024	Sterilization of health care products – Moist heat – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices.

[2] Note that no data from real-world evidence analyses and device registries is available with the clinical use of VitriFreeze ES/VitriThaw ES for vitrification of zygotes. Therefore, clinical safety and performance of VitriFreeze ES/VitriThaw ES for these intended uses was based on equivalence to respectively:

- *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.*

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
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 13408-1:2023 / EN ISO 13408-1:2024	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 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.
Ph. Eur. 0255	European Pharmacopoeia monograph 0255 – Human albumin solution

9 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.4	12/01/2022	Initial validated version	Version A.4 is validated by the Notified Body Validation language: English
A.5	13/06/2022	Update 2022	Not submitted for validation, as there were no significant changes that required validation.
A.6	31/05/2023	Update 2023	Not submitted for validation, as there were no significant changes that required validation.
A.7	29/04/2024	Update 2024	Not submitted for validation, as there were no significant changes that required validation.
A.8	30/04/2025	Update 2025	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 since the device is for professional use only.