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 kit
VitriFreeze ES/VitriThaw ES 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

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

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

2012

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

The VitriFreeze (ES) /VitriThaw (ES) kit are used to store embryos before assisted reproduction treatments (either IVF, ICSI or embryo transfer), to preserve embryos before therapy for malignant diseases or surgical infertility treatments and to ensure the recovery of small number of embryos in severe female or male infertility. Therefore, embryo vitrification is an important component of fertility management and is routinely used in ART clinics/andrology labs.

Direct physical contact only occurs between the media products and human 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 VitriFreeze (ES)/VitriThaw (ES) of FertiPro NV for the vitrification and thawing of human embryos.

3 Device description

3.1 Description of the device

The VitriFreeze (ES)/VitriThaw (ES) kits are sets of ready-to-use media for vitrification and warming of human 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. VitriFreeze (ES)/VitriThaw (ES) are DMSO/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 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 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 (ES)/VitriThaw (ES) 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 VitriFreeze (ES)/VitriThaw (ES) are identified.

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

VitriFreeze (ES)/VitriThaw (ES) are intended to be used with the following devices:

- Vitrification device, preferably closed system (VitriFreeze (ES)™/VitriThaw (ES)™ were clinically validated with use of the following closed devices: High Security Vitrification straw (HSV; CBS) or Vitrisafe (Nextclinics). Importantly, each laboratory should validate their own procedures when using VitriFreeze (ES)™/VitriThaw (ES)™ in combination with other vitrification devices)
- 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 Human Serum Albumin in VitriFreeze (ES)/VitriThaw (ES). A potential risk associated with Human Serum Albumin 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 VitriFreeze (ES)/VitriThaw (ES) 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 VitriFreeze (ES)/VitriThaw (ES) is restricted to the vitrification and warming of human 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 VitriFreeze (ES)/VitriThaw (ES) is clear:

- Stabilization of the cell membrane of the embryo in the medium
- Carrier and source of essential molecules needed by the embryo
- Detoxification by binding waste products from cell metabolism.
- Facilitating 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 VitriFreeze (ES)/VitriThaw (ES) for vitrification and warming of human 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. 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 (ES)/VitriThaw (ES) 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 on a yearly basis, to investigate whether clinical ART data (pregnancy and delivery rates) obtained during the search are consistent with the clinical outcomes described in the most recent benchmark paper from the ESHRE (European Society of Human Reproduction and Embryology) (Wyns et al. 2022):

In vitro fertilization (IVF)*:	**Intra cytoplasmic sperm injection (ICSI)*:**	**Frozen embryo transfer (FET):**
- 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%)*	- 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%**	- 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%**

-Delivery rate per transfer: **26.4%** *(range: 14.2 – 38.7%)*	*(range: 9.3 – 37.3%)*	*(range: 17.1 – 41.4%)*

*Values generally without freezing of embryo

When it concerns the embryological parameters, the values should be consistent with the competency limits as reported by the Alpha Scientists in Reproductive Medicine (Alpha Scientists In Reproductive Medicine 2012) or the ESHRE Special Interest Group of Embryology (ESHRE Special Interest Group of Embryology 2017):

Zygote minimal competence limits:	**Embryo minimal competence limits:**	**Blastocyst minimal competence limits values**
- Morphological survival rate: *≥70%* *- Cleavage rate (calculated as* $\frac{\text{no. of cleaved embryos Day 2}}{\text{no. } \frac{2PN}{2PB} \text{oocytes on Day 1}}$ *x 100):* ≥95% *- Day 2 embryo development rate (calculated as* $\frac{\text{no. 4-cell embryo on Day 2}}{\text{no. normally fertilized oocytes}}$ *x 100):* ≥50% *- Day 3 embryo development rate (calculated as* $\frac{\text{no. 8-cell embryo on Day 3}}{\text{no. normally fertilized oocytes}}$ *x 100):* ≥45% *- Implantation rate cleavage stage (calculated as* $\frac{\text{no. sacs seen on ultrasound}}{\text{no. embryos transferred}}$ *x 100):* ≥25%, 10-30% (relative) lower is acceptable	*- Morphological survival rate (fully intact):* *≥70%* *- Morphological survival rate (≥ 50% intact):* *≥85%* *- Day 3 embryo development rate (calculated as* $\frac{\text{no. 8-cell embryo on Day 3}}{\text{no. normally fertilized oocytes}}$ *x 100):* ≥45%, 10% (relative) lower is acceptable *- Implantation rate cleavage stage (calculated as* $\frac{\text{no. sacs seen on ultrasound}}{\text{no. embryos transferred}}$ *x 100):* ≥25%, 10% (relative) lower is acceptable	- Survival rate: ≥90%, 10% lower is acceptable *- Implantation rate cleavage stage (calculated as* $\frac{\text{no. sacs seen on ultrasound}}{\text{no. blastocysts transferred}}$ *x 100):* ≥35%, 10% (relative) lower is acceptable

There were 10 articles retrieved in literature studying the performance of VitriFreeze (ES)/VitriThaw (ES) is indicated in the table below. Overall it can be concluded from these papers that ART outcomes, when VitriFreeze (ES)/VitriThaw (ES) is used for embryo vitrification, are consistent with the clinical ART outcomes described in the benchmark paper from the ESHRE (most recent report: (Wyns et al. 2022)) and/or the reported embryological parameters are consistent with the competency limits reported by the Alpha Scientists in Reproductive Medicine (Alpha Scientists In Reproductive Medicine 2012) or the ESHRE Special Interest Group of Embryology (ESHRE Special Interest Group of Embryology 2017).

5.2 Device registries

ART outcomes generated in IVF clinics over the world are included in the clinical evaluation report of VitriFreeze (ES)/VitriThaw (ES). It involves data from an IVF clinic in Austria of 1472 warming cycles, another IVF clinic in Europe of 358 warming cycles and an IVF clinic in South-Africa of 493 cycles

The reported pregnancy/delivery rates of the IVF clinic, using VitriFreeze ES/VitriThaw ES in combination with the VitriSafe carrier, are consistent with the ESHRE reference values for FER (Wyns et al. 2021). Also, the reported embryological parameters are consistent with the competency limits reported by the Alpha Scientists in Reproductive Medicine (Alpha Scientists In Reproductive Medicine 2012) or the ESHRE Special Interest Group of Embryology (ESHRE Special Interest Group of Embryology 2017). These results indicate that VitriFreeze ES/VitriThaw ES is safe and effective for the vitrification of 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

VitriFreeze (ES)/VitriThaw (ES) functions as stated by the manufacturer: i.e. vitrification and thawing of human embryos[1].

This is established by clinical data which demonstrate that pregnancy and delivery rates of procedures in which VitriFreeze (ES)/VitriThaw (ES) is used for embryo vitrification are consistent with the published outcomes as reported by the ESHRE (most recent report: (Wyns et al. 2022)), and/or by data showing that the embryological parameters of embryos vitrified/warmed with VitriFreeze (ES)/VitriThaw (ES) are consistent with the competency limits reported by the Alpha Scientists in Reproductive Medicine (Alpha Scientists In Reproductive Medicine 2012) or the ESHRE Special Interest Group of Embryology (ESHRE Special Interest Group of Embryology 2017).

Moreover, there is no evidence from the clinical data, as well as from the registered complains, market/customer feedback and/or vigilance that VitriFreeze (ES)/VitriThaw (ES) is toxic for embryos, 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 post-market clinical follow-up

Post-market clinical follow-up for VitriFreeze (ES)/VitriThaw (ES) (including PMCF for the HSA component included in 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 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 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 more recently developed vitrification technique for which VitriFreeze/Thaw and VitriFreeze ES/VitriThaw ES are designed. The procedure for successful cryopreservation by vitrification of embryos has been the subject of intense research over many years. Based on scientific literature, it is concluded that vitrification is a similar or even a better and safer option for cryopreservation when compared to slow freezing. Devices with similar intended use as VitriFreeze (ES)/VitriThaw (ES) are available on the European Union or international markets.

7 Suggested profile and training for users

VitriFreeze (ES)/VitriThaw (ES) is used in specialized laboratories performing fertilization techniques, such as IVF and ICSI. The intended users are ART professionals (including lab technicians, embryologists, or medical doctors).

[1] 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.*

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 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) ISO 20417:2021**: Medical devices: information supplied by the manufacturer
- **ISO 10993-1:2018**: 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.
- **(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)
- **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 .
- **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 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.1	22/06/2021	Initial version	Date: not yet Validation language: English

A.2	13/09/2021	Small changes before MDR conformity assessment	Date: not yet Validation language: English
A.3	13/12/2021	MDR conformity assessment round 1	Date: not yet Validation language: English
A.4	12/01/2022	MDR conformity assessment round 2	Version A.4 is validated by the Notified Body Validation language: English
A.5	13/06/2022	Update 2022	Date: not yet Validation language: English
A.6	31/05/2023	Update 2023	Not submitted for validation, as there were no significant changes that required validation.

10 Validation language: English 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.

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.

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.