

Summary of Safety and Clinical Performance

SpermFreeze (with phenol red) / SpermFreeze SSP

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)

SpermFreeze
SpermFreeze with phenol red
SpermFreeze SSP

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

SpermFreeze SSP: 5411967SPF152
SpermFreeze (with phenol red): 5411967SPFWT147

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 devices according to Annex VIII of the MDR

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

SpermFreeze: 2012
SpermFreeze with phenol red: 2016
SpermFreeze SSP: 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

SpermFreeze (with phenol red) and SpermFreeze SSP are used for cryopreservation of human sperm for further use in Assisted Reproductive Technologies (ART). SpermFreeze (with phenol red) can also be used for the cryopreservation of sperm from testicular biopsies (TESE).

2.2 Indication(s) and intended patient groups

- **Indications for use:** SpermFreeze (with phenol red) and SpermFreeze SSP are used
 - to store donor and partner spermatozoa before assisted reproduction treatments (either IUI, IVF or ICSI);
 - to preserve spermatozoa before therapy for malignant diseases, vasectomy or surgical infertility treatments;
 - to ensure the recovery of small number of spermatozoa in severe male factor infertility.
- **Intended users:** SpermFreeze (with phenol red) and SpermFreeze SSP are used in specialized laboratories performing fertilization techniques, including IVF, ICSI and sperm preparation/analysis. The intended users are ART-professionals (lab technicians, embryologists, or medical doctors).
- **Intended patient populations:** SpermFreeze (with phenol red) and SpermFreeze SSP are used to store donor and partner spermatozoa during ART-procedures of patients and/or couples undergoing infertility treatments.

2.3 Contraindications and/or limitations

There are no known contraindications and/or limitations identified for Sperm Freezing media.

3 Device description

3.1 Description of the device

- For the principle of operation, reference is made to the IFU: FP09 I11 R01 and FP09 I11 SSP R01.
- Sperm Freezing media are not intended for single use. Multiple single-procedures can be performed. 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).
- Sperm Freezing media are sterilized using aseptic processing techniques (filtration).
- Sperm Freezing media consist of water, salts, glycine and cryoprotectants (i.e. glycerol, sucrose and Human Serum Albumin) to protect sperm during cryopreservation. The inclusion of Human Serum Albumin (which is a medicinal substance derived from human blood plasma) in ART media from FertiPro is approved by the EMA (European Medicine Agency).
- Direct physical contact occurs between the media products and the human sperm cell. The medium does not come into contact with the human body.
- The lifetime for Sperm Freezing media is at least 10 years.

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

The following accessory is defined for SpermFreeze media: SpermFreeze Box.

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

Sperm Freezing media are intended to be used with the following devices:

- Sperm freezing straws (e.g. CBS high security sperm straws, classified as Class IIa Medical Devices)
- Freezing tank with liquid nitrogen

4 Risks and warnings

4.1 Residual risks and undesirable effects

The output from the clinical evaluation report and of the clinical evaluation outcome report of HSA are taken into account in the risk management file of Sperm Freezing media in order to determine the benefits/risk ratio.

The only remaining residual risk is the inclusion of Human Serum Albumin in Sperm Freezing media. The inclusion of this medicinal substance derived from human blood plasma in the devices is approved by the EMA.

The major benefit of HSA in Sperm Freezing media is clear:

- Inhibition of lipid peroxidation that can be damaging to sperm.
- Detoxification by binding waste products from cell metabolism.
- HSA prevents cell aggregation and adherence to laboratory equipment and promotes the ease of gamete handling and manipulation.

A potential risks of HSA in Sperm Freezing media are:

- **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 human sperm survival assays are routinely performed as part of Sperm Freezing media 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, Alunorm 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 Sperm Freezing media is restricted to the cryopreservation of human sperm 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.

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 Sperm Freezing media for cryopreservation of human sperm 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
- Do not re-sterilize after opening
- Aseptic technique should be used to avoid possible contamination. Sperm Freezing media do 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 SpermFreeze (with phenol red) / SpermFreeze SSP were needed.

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

5.1 Real-word 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 from the European Society of Human Reproduction and Embryology (ESHRE):

- Embryological outcomes:

<i>ESHRE Special Interest Group of Embryology, 'The Vienna consensus: report of an expert meeting on the development of art laboratory performance indicators', Hum Reprod Open, 2017: hox011.</i>	<p>ICSI normal fertilization rate: $\geq 65\%$ (lower range: 55%)</p> <p>IVF normal fertilization rate: $\geq 60\%$ (lower range: 50%)</p> <p>Blastocyst development rate: $\geq 40\%$ (lower range: 30%)</p>
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- Clinical ART outcomes:

<i>Smeenk, J., C. Wyns, C. De Geyter, M. Kupka, C. Bergh, I. Cuevas Saiz, D. De Neubourg, K. 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.</i>	In vitro fertilization (IVF):	Intra cytoplasmic sperm injection (ICSI):	Frozen embryo transfer (FET):	Intrauterine insemination (IUI):
	Clinical pregnancy rate per aspiration: 18.4 – 53.1%	Clinical pregnancy rate per aspiration: 16.0 – 46.1%	Pregnancy rate per thawing: 22.5 – 50.1%	Delivery rate per cycle (using husband semen IUI-H): 1.9 – 23.1%
	Clinical pregnancy rate per transfer: 27.4 – 63.0%	Clinical pregnancy rate per transfer: 26.9 – 52.1%	Pregnancy rate per transfer: 22.5 – 56.0%	Delivery rate per cycle (using donor semen IUI-D): 6.5 – 27.9%
	Delivery rate per aspiration: 23.3 – 29.4%	Delivery rate per aspiration: 10.6 – 28.6%	Delivery rate per thawing: 7.2 – 41.4%	
	Delivery rate per transfer: 17.9 – 45.9%	Delivery rate per transfer: 12.1 – 39.4%	Delivery rate per transfer: 8.4 – 42.4%	

Note that there are no general accepted embryology /ART outcomes are defined after the use of cryopreserved TESE samples during ART, therefore following approach is used for such samples:

- Embryology and ART outcomes should not be significantly lower than the outcomes with the fresh TESE samples.
- Embryology and ART outcomes should not be significantly lower than the outcomes with the comparable medium.

cycles (covering the time period from 1 January to 31 December 2018) and is summarized in the table below:

A literature search is performed on a yearly basis, to investigate whether sperm parameter outcomes obtained during the search are consistent with acceptable outcomes, based on results found in the literature:

- a reduction in sperm motility is set on 50-60% after cryopreservation with SpermFreeze media*

- a reduction in sperm vitality is set on 50% after cryopreservation with SpermFreeze media*
- effect on sperm DNA fragmentation is comparable with that of similar devices with identical intended use as SpermFreeze media on the market
- fertilization potential of sperm cryopreserved with SpermFreeze media is comparable with that of fresh sperm

* In case of a comparative study with similar devices with identical intended use as Sperm Freezing media: the reduction of sperm motility/vitality is not significantly lower than the reduction in sperm motility/vitality of the cryopreservation media of competitors.

Sperm vitality, motility and Sperm DNA fragmentation are important parameters to evaluate the quality of the spermatozoa upon cryopreservation, but importantly, reduction of these parameters do not exclude that the thawed semen sample will result in a successful ART procedure. Based on these parameters, the physician will determine which ART, i.e. IUI, IVF or ICSI, will be used to have the highest chance to succeed. As indicated above, the ICSI technique circumvents the natural selection process in fertilization and enables the successful use of spermatozoa with severely impaired characteristics to achieve clinical pregnancy. The devices included in this clinical evaluation report are for professional use only, and do need the knowledge of these professionals to interpret the semen samples upon thawing.

An overview of the articles studying the performance of Sperm Freezing media is indicated in the table below. It can be concluded from these papers that embryological and ART outcomes, when Sperm Freezing media are used, are consistent with the clinical outcomes described in the benchmark papers. Also the effects on motility, viability, DNA fragmentation and fertilization potential after cryopreservation of sperm with Sperm Freezing media are within acceptable limits and comparable with other products on the market.

Selected articles describing the performance and/or safety of Sperm Freezing media ¹				
(Zribi et al. 2010)	(Prisant et al. 2010)	(Fabozzi et al. 2016)	(Santonastaso et al. 2021)	(Khosronezhad et al. 2023)
(Thomson et al. 2009)	(Rahana et al. 2011)	(Lusignan et al. 2018)	(Kumari et al. 2021)	(Cheredath et al. 2023)
(Donnelly, McClure, and Lewis 2001)	(Freour et al. 2012)	(El-Ahwany, Samir, and Alahwany 2018)	(Tvrda et al. 2021)	(Cakrasana et al. 2022)
(Vutyavanich, Piromlertamorn, and Nunta 2010)	(Ahmad et al. 2010)	(Awaga et al. 2019)	(Dayal et al. 2021)	(Moungala 2023)
(Punyatanasakchai et al. 2008)	(Satirapod et al. 2012)	(Reignier et al. 2018)	(Hosseinmardi et al. 2021)	(Al-Obeidy, Akkila, and Noel 2023)
(Desrosiers et al. 2006)	(Zribi et al. 2012)	(O'Neill et al. 2019)	(Hezavehei et al. 2022)	(Albari Shimal, Abdulwahid Mohammed, and Al-Essawe 2023)
(Bhattacharya et al. 2006)	(Moubasher et al. 2013)	(Taher-Mofrad et al. 2020)	(Androni et al. 2021)	(Falah 2019)
(Bandularatne and Bongso 2002)	(Bizet et al. 2012)	(Valipour et al. 2020)	(Karacan et al. 2013)	(Juanpanich et al. 2022)
(Donnelly et al. 2001)	(Gatimel, Leandri, and Parinaud 2013)	(Tvrda et al. 2020)	(Arciero et al. 2022)	(Baharsaadi et al. 2024) (article u10-5)

¹ 3 additional articles were retrieved that describe the safety and performance of Sperm Freezing media. 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.

Selected articles describing the performance and/or safety of Sperm Freezing media ¹				
(O'Connell, McClure, and Lewis 2002)	(Boitrelle et al. 2012)	(Karthikeyan et al. 2019)	(Ghantabpour et al. 2022)	(Ortiz-Vallecillo et al. 2024) (article u10-42)
(Saritha and Bongso 2001)	(Philippon et al. 2015)	(Seifi et al. 2020)	(Moungala 2022)	
(Menon et al. 2009)	(Tongdee et al. 2015)	(Hezavehei et al. 2021)	(Ali and Al-Essawe 2022)	
(Konc, Kanyo, and Cseh 2008)	(Montagut et al. 2015)	(Valipour et al. 2021)	(Evgeni et al. 2022)	

5.2 Device registries

Clinical data on more than 600 cycles (IVF and ICSI cycles) is obtained from IVF centers in Europe that use Sperm Freezing media. Embryological and ART outcomes of these clinics are consistent the published outcomes as reported by the Vienna consensus group and the ESHRE.

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

Cryopreservation of human semen samples is an essential step in the management of fertility and is routinely used in ART clinics and andrology labs. Despite the success of this technique, cryopreservation of semen samples is associated with damage to the frozen/thawed semen sample, which is inherent to the cryopreservation method. An optimal cryopreservation method for human spermatozoa which would circumstance these advantages is not yet determined. With this in mind, it is important to evaluate the damaging effects after cryopreservation with Sperm Freezing media and to evaluate if these effects are comparable with other cryopreservation media on the market. The main damaging effects after cryopreservation are decreased motility, decreased viability and increased DNA fragmentation.

All these aspects are studied in the clinical evaluation report of the Sperm Freezing media. It could be concluded that Sperm Freezing media function as stated by the manufacturer and that no complications or problems have been reported.

This is established by clinical data which demonstrate that

- ART/embryology outcomes (from literature or received from IVF clinic) of procedures in which the Sperm Freezing media are used fall within the normal range of published outcomes as reported by the ESHRE.
- ART/embryology outcomes (from literature or received from IVF clinic) of procedures in which SpermFreeze (with phenol red) is used for TESE samples are not significantly lower than the outcomes with the fresh TESE samples.
- The results found in literature are within the acceptable defined outcomes concerning the different sperm parameters (motility, vitality, DNA fragmentation and fertilization potential).
- The results regarding motility and vitality found in literature are not significantly lower than the results from cryopreservation media of competitors.

Moreover, there is no evidence from the clinical data, as well as from the registered complains, market/customer feedback and/or vigilance that Sperm Freezing media are toxic for gametes and

embryos, nor that the media have risk for mutagenity, oncogenicity, teratogenicity, carcinogenicity, cytotoxicity, allergenicity and irritancy for patients and users.

5.5 Ongoing or planned PMS/PMCF

PMS/PMCF for Sperm Freezing media (including PMS/PMCF for the HSA component included in Sperm Freezing media) 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 is a necessary tool in ART. Two different methods, i.e. conventional slow-freezing and vitrification of spermatozoa exist. Conventional slow-freezing as performed with Sperm Freezing media is still the most commonly used technique and almost all products currently on the market by competitors are based on this technique.

Sperm vitrification is described in literature but is still under development, and does have some remaining challenges to tackle. This is reflected in the fact that no commercial media are currently available on the market for sperm vitrification.

7 Suggested profile and training for users

Sperm Freezing media are used in specialized laboratories performing fertilization techniques, including IVF, ICSI and sperm preparation/analysis. The intended users are IVF professionals (lab technicians, embryologists, or medical doctors).

8 Reference to any applicable common specification(s), harmonized standard(s) or applicable guidance document(s)

The following technical standards apply to Sperm Freezing media:

MDR 2017/745	European Medical Device Regulation 2017/745 of 5 April 2017.
(EN) ISO 13485:2016 (Amd 11:2021)	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.
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.
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 (Amd 11:2021)	Medical devices – Application of risk management to medical devices.
(EN) ISO 15223-1: 2021	Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements.

(EN) ISO 17665-1:2006	Sterilization of health care products – Moist heat – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices.
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) ISO 11737-1:2018, A1:2021	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 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.6	04/06/2021	Remarks BSI question round 3 on SSCP	Version A.6 is validated by the Notified Body Validation language: English
A.7	03/02/2022	Update 02-2022	Not submitted for validation, as there were no significant changes that required validation.
A.9	16/10/2023	Update 2023	Not submitted for validation, as there were no significant changes that required validation.
A.10	08/02/2024	-Addition of an accessory: SpermFreeze Box - Broaden the intended use of SpermFreeze (with phenol red)	Version A.10 is validated by the Notified Body Validation language: English
A.11	16/10/2024	Update 2024	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 as the device is for professional use only.