Summary of safety and clinical performance: SpermFreeze Solution™

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 intended users or patients.

The following information is intended for users/healthcare professionals.

1 Device identification and general information

1.1	Device trade name	SpermFreeze Solution
1.2	Manufacturer's name and address	Vitrolife Sweden AB, Gustaf Werners gata 2, 421 32 Västra Frölunda, Sweden
1.3	Manufacturer's single registration number (SRN)	SE-MF-000002389
1.4	Basic UDI-DI	735002591ABCDH
1.5	Global Medical Device Nomenclature (GMDN) code	44046
1.6	Class of device	Class III
1.7	Year when the first certificate (CE) was issued covering the device	2010
1.8	Authorized representative if applicable; name and SRN	Not applicable
1.9	NB's name (the NB that will validate the SSCP) and the NB's single identification number	DNV Product Assurance AS, Veritasveien 1, 1363 Høvik, Norway 2460

2 Intended use of the device

2.1 Intended purpose

SpermFreeze Solution is a medical device intended for use in assisted reproductive technology (ART) for cryopreservation of human sperm.

2.2 Indication and target population

SpermFreeze Solution: Medium for cryopreservation of human sperm.

The target patient population is an adult or reproductive-age population that undergoes *in vitro* fertilization (IVF) treatment or fertility preservation.

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2.3 Contraindications and/or limitations

SpermFreeze Solution contains gentamicin. Do not use in patients with known hypersensitivity/allergy to the component. (However, according to the Indication for Use, SpermFreeze Solution does not have patient contact.)

3 Device description

3.1 Description of the device

SpermFreeze Solution is a bicarbonate and MOPS buffered medium intended to support cryopreservation of human sperm. Based on its Indication for Use, SpermFreeze Solution will have gamete contact.

The device is sterile filtered using aseptic technique. SpermFreeze Solution is stable until the expiry date shown on the container labels and the LOT-specific Certificate of Analysis. Media bottles can be used for up to two weeks after first opening, use aseptic technique and minimize the time outside the refrigerator. Record opening date on the bottle. Discard excess media no later than two weeks after first opening. Based on regulatory guidelines, the medicinal components present in SpermFreeze Solution are gentamicin and human serum albumin (HSA). Gentamicin is an antibiotic that could result in sensitization or allergic reaction in the patient or user.

Figure 1. SpermFreeze Solution

3.2 A reference to previous generation(s) or variants if such exists, and a description of the differences

There have been no previous versions of SpermFreeze Solution on the market.

3.3 Description of any accessories which are intended to be used in combination with the device

Not applicable.

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

General equipment and sterile non-toxic disposables for the IVF lab including freezing machine, G-IVF PLUS, storage device and storage system.

4 Risks and warnings

4.1 Residual risks and undesirable effects

After mitigation, there are two unacceptable residual risks due to the presence of HSA, with the hazardous situations, “Patient exposed to contaminated human serum albumin (HSA)” and “User exposed to contaminated human serum albumin (HSA)”. However, according to the Indication for Use, SpermFreeze Solution does not have contact with the patient. The end user (IVF professional) is expected to follow the ESHRE revised guidelines for good practice in IVF laboratories and use the device according to its IFU. The benefit-risk analysis of these risks concluded that the benefits of including HSA in SpermFreeze Solution outweigh the risks associated with blood-borne contamination. No case reports of allergic/hypersensitivity reactions or infections associated with HSA during ART procedures have been reported. No adverse events or undesirable side-effects have been reported for the device during its time on the market. To control risks, raw materials for SpermFreeze Solution are quality tested and each LOT of the final product is tested for pH, osmolality, sterility, bacterial endotoxins, and human sperm survival. Additionally, the user is informed about the device components, contraindication, and precautions by providing information on labels and the Instruction for Use.

All the clinical risks that could occur during the use of SpermFreeze Solution are presented in below.

Effect	Hazardous situation
Patient	Patient exposed to contaminated human serum albumin (HSA)*
End user	Allergic user exposed to gentamicin
	User exposed to gentamicin
	User exposed to human serum albumin (HSA)
	User exposed to contaminated human serum albumin (HSA)*

*Unacceptable residual risks. All other clinical risks are acceptable after risk control measures.

4.2 Warnings and precautions

Precautions related to the use of SpermFreeze Solution are listed.

- Discard product if bottle integrity is compromised. Do not use SpermFreeze Solution if it appears cloudy.
- SpermFreeze Solution contains human serum albumin.
- Caution: All blood products should be treated as potentially infectious. Source material from which this product was derived was found negative when tested for antibodies to HIV, HBc, HCV, and HTLV I/II and non-reactive for HbsAg, HCV RNA and HIV-1 RNA and syphilis. No known test methods can offer assurance that products derived from human blood will not transmit infectious agents.

- To avoid contamination Vitrolife strongly recommends that media should be opened and used only with aseptic technique.
- The risks of reproductive toxicity and developmental toxicity for IVF media, including Vitrolife's IVF media, have not been determined and are uncertain.
- Any serious incident that has occurred in relation to the device should be reported to the manufacturer.
- Not for injection.
- Discard the product according to standard clinical practice for medical hazardous waste when the procedure is finished.

4.3 Other relevant aspects of safety, including a summary of any field safety corrective action (FSCA including FSN) if applicable

No FSCAs have been taken for SpermFreeze Solution during its lifecycle.

5 Summary of clinical evaluation and post-market clinical follow-up

5.1 Summary of clinical data related to equivalent device, if applicable

Not applicable.

5.2 Summary of clinical data from conducted investigations of the device before the CE-marking, if applicable

No pre-market clinical investigations were performed.

5.3 Summary of clinical data from other sources, if applicable

A systematic literature search was conducted to identify clinical data on the safety and performance of SpermFreeze Solution. Several studies confirm post-thaw sperm recovery (viability, motility) at normal rates after the use of SpermFreeze Solution [1-15]. Clinical pregnancy rates (CPRs) reported after use of SpermFreeze Solution [13, 16] generally align with the European results published by ESHRE [17]. Two references reported data on live births after use of SpermFreeze Solution [13, 16]. According to the results from the literature search, no deviation was found in the safety or performance of the device. No post-market clinical follow-up (PMCF) studies have been conducted for SpermFreeze Solution. However, results from a PMCF end user survey confirm the safety and performance of SpermFreeze Solution and ensure the continued acceptability of the benefit-risk ratio. No emerging risks or unknown side-effects were identified, and no known side-effects and/or contraindications were found. SpermFreeze Solution has been on the market since 2010, and no non-serious incidents or undesirable side-effects were identified after its use with a frequency or severity that negatively impact its benefit-risk profile.

5.4 An overall summary of the clinical performance and safety

According to the Indication for Use, the clinical benefit of SpermFreeze Solution is as medium to support cryopreservation of sperm. Several studies confirm post-thaw sperm recovery (viability, motility) at normal rates after the use of SpermFreeze Solution [1-15]. CPRs reported after use of SpermFreeze Solution [13, 16] generally align with the yearly European results published by ESHRE [17]. Data from post-market surveillance, including a PMCF end user survey, and risk management also support the safety and performance of SpermFreeze Solution. There are no indications of any negative effects from use of SpermFreeze Solution. As identified in the risk management documents, two residual risks due to the presence of HSA are unacceptable. However, after benefit-risk evaluation,

the benefits of using HSA in the device outweighs the risks associated with blood-borne contamination. All other risks are acceptable after risk control measures. According to the results of the literature search, the risk of an allergic/hypersensitivity reaction (or infection) associated with HSA, gentamicin or antibiotics when used for ART procedures is low. No new risks have been identified or are expected when the device is used according to its Indications for Use. Therefore, the benefit-risk profile is acceptable according to current knowledge/state of the art.

5.5 Ongoing or planned post-market clinical follow-up

There are no ongoing or planned PMCF studies for SpermFreeze Solution. However, general PMCF procedures, such as screening of scientific literature, searching adverse event databases and performing a PMCF end user survey will be performed.

6 Possible diagnostic or therapeutic alternatives

ART is a treatment option for patients unable to conceive naturally as well as patients who have tried other treatments such as medications and surgical procedures without success. There are no therapeutic alternatives for patients at this stage.

Fertility preservation can serve as a therapeutic alternative for patients undergoing ART, offering a proactive measure to safeguard reproductive potential, particularly in cases where medical conditions or treatments may impact fertility.

Sperm cryopreservation is an important technique for fertility management in ART. Slow freezing is still the conventional method for cryopreserving sperm. Devices with similar intended use as SpermFreeze Solution are available in the European Union or other international markets.

7 Suggested profile and training for users

The end user (IVF professional) is expected to be trained and qualified within the ART field and use the device according to its IFU. As no special design feature or safety concerns were identified SpermFreeze Solution, no specific training is required for end-users.

8 Reference to any harmonized standards and common specifications applied

- Medical Devices Regulation (EU) 2017/745 (MDR)
- EN ISO 13485:2016. Medical devices — Quality management systems — Requirements for regulatory purposes
- EN ISO 14971:2019. Medical devices — Application of risk management to medical devices
- 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
- ISO/TR 20416:2020. Medical devices — Post-market surveillance for manufacturers
- EN ISO 20417:2021. Medical devices — Information to be supplied by the manufacturer
- MEDDEV 2.7/1 revision 4. Clinical evaluation – A guide for manufacturers and notified bodies under Directives 93/42/EEC and 90/385/EEC. June 2016
- MDCG 2020-6 Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies. April 2020

- MDCG 2019-9 Rev.1. Summary of safety and clinical performance. A guide for manufacturers and notified bodies. March 2022

The conformity assessment will be performed according to the procedure outlined in Annex IX of the MDR (EU) 2017/745.

9 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
1	2021/09/02	Initial version of SSCP for SpermFreeze Solution (REP-4070-v.1.0)	
2	2022/08/24	Annual update of SSCP for SpermFreeze Solution (REP-4070-v.2.0)	
3	2023/02/13	Address DNV clinical NCs	☑ Yes Validation language: English
4	2023/10/23	Annual update of SSCP for SpermFreeze Solution (REP-4070-v.4.0)	
5	2024/07/02	Annual update of SSCP for SpermFreeze Solution (REP-4070-v.5.0)	
6	See publish date	Edit Section 6 of SSCP for SpermFreeze Solution (REP-3365-v.6.0)	☑ Yes Validation language: English

10 References

1. Kishimoto M, Mizuta, S., Higashiyama, R., Yamaguchi, K., Kitaya, K., Matsubayashi, H. and Ishikawa, T.: Comparison of the rate of motile testicular sperm after a freeze-thaw process among cryoprotective agetns from three manufacturers. *JSRM meeting book* 2018.
2. Lu X, Zhang Y, Bai H, Liu J, Li J, Wu B: Mitochondria-targeted antioxidant MitoTEMPO improves the post-thaw sperm quality. *Cryobiology* 2018, 80:26-29.
3. Le MT, Nguyen TTT, Nguyen TT, Nguyen VT, Nguyen TTA, Nguyen VQH, Cao NT: Cryopreservation of human spermatozoa by vitrification versus conventional rapid freezing: Effects on motility, viability, morphology and cellular defects. *Eur J Obstet Gynecol Reprod Biol* 2019, 234:14-20.
4. Le MT, Nguyen TTT, Nguyen TT, Nguyen TV, Nguyen TAT, Nguyen QHV, Cao TN: Does conventional freezing affect sperm DNA fragmentation? *Clin Exp Reprod Med* 2019, 46(2):67-75.
5. Li S, Ao L, Yan Y, Jiang J, Chen B, Duan Y, Shen F, Chen J, Inglis B, Ni R *et al*: Differential motility parameters and identification of proteomic profiles of human sperm cryopreserved with cryostraw and cryovial. *Clin Proteomics* 2019, 16:24.
6. Nakata K, Yoshida K, Yamashita N: Preclinical evaluation of a new cryopreservation container for a limited number of human spermatozoa. *J Reprod Dev* 2019, 65(4):297-304.
7. Ibis E, Hayme S, Baysal E, Gul N, Ozkavukcu S: Efficacy and safety of papaverine as an in vitro motility enhancer on human spermatozoa. *J Assist Reprod Genet* 2021, 38(6):1523-1537.
8. Tas DO, Ozkavukcu S, Inanc I, Kose SK, Erdemli E: The effects of coenzyme Q10 and curcumin supplementation in freezing medium for human sperm cryopreservation. *Eur J Obstet Gynecol Reprod Biol* 2023, 287:36-45.
9. Saadat Maryan H, Ghasemian F, Bahadori MH: Effects of cryopreservation in the presence of Natural Deep Eutectic Solvents (NADESs) on sperm parameters. *Cryobiology* 2023, 112:104550.
10. Moradi B, Faramarzi A, Ghasemi-Esmailabad S, Aghaz F, Hashemian AH, Khazaei M: L-proline as a novel additive to cryopreservation media improved post-thaw quality of human spermatozoon via reducing oxidative stress. *Andrologia* 2022, 54(1):e14301.
11. Javanmard F, Bidmeshkipour A, Ghasemian Yadegari J: Ceratonia siliqua L improved cryodamage of asthenozoospermic specimens: An experimental study. *Int J Reprod Biomed* 2022, 20(12):1029-1038.
12. Alqawasmeh OA, Zhao M, Chan CP, Leung MB, Chow KC, Agarwal N, Mak JS, Wang CC, Pang CP, Li TC *et al*: Green tea extract as a cryoprotectant additive to preserve the motility and DNA integrity of human spermatozoa. *Asian J Androl* 2021, 23(2):150-156.
13. Sugihara A, Punjabi U, Chimienti T, Goovaerts I, Peeters K, Bouziotis J, De Neubourg D: Sperm DNA Fragmentation after Cryopreservation and Sperm Selection Has No Implications for Clinical Pregnancies and Live Births after Intrauterine Insemination with Donor Sperm. *J Pers Med* 2023, 13(12).

14. Karakus FN, Kuran SB, Solakoglu S: Effect of curcumin on sperm parameters after the cryopreservation. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2021, 267:161-166.
15. Jahanseir F, Ghasemian F, Zahiri Z: Aquaporin expression in cryopreserved human sperm: exploring the capabilities of natural deep eutectic solvents (NADEs). *Cryo Letters* 2024, 45(3):158-167.
16. Klami R, Tomas C, Mankonen H, Perheentupa A: ICSI outcome after microdissection testicular sperm extraction, testicular sperm aspiration and ejaculated sperm. *Reprod Biol* 2024, 24(1):100825.
17. Smeenk J, Wyns C, De Geyter C, Kupka M, Bergh C, Cuevas Saiz I, De Neubourg D, Rezabek K, Tandler-Schneider A, Rugescu I *et al*: ART in Europe, 2019: results generated from European registries by ESHRE. *Hum Reprod* 2023, 38(12):2321-2338.