Doc. ID:	Version:	Publish date:
REP-3338	5.0	2025/02/20

Summary of safety and clinical performance FreezeKit™ Cleave/ThawKit™ Cleave

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	FreezeKit Cleave/ThawKit Cleave
1.2	Manufacturer's name and address	Vitrolife Sweden AB, Gustaf Werners gata 2, SE-421 32 Västra Frölunda, Sweden
1.3	Manufacturer's single registration number (SRN)	SE-MF-000002389
1.4	Basic UDI-DI	FreezeKit™ Cleave: 735002591ABFDP ThawKit™ Cleave: 735002591ABHDT
1.5	Global Medical Device Nomenclature (GMDN) code	42850
1.6	Class of device	Class III
1.7	Year when the first certificate (CE) was issued covering the device	2012
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	Det Norske Veritas (DNV) Product Assurance AS Veritasveien 1, 1363 Høvik Norway 2460

2 Intended use of the device

2.1 Intended purpose

FreezeKit Cleave and ThawKit Cleave are medical devices intended for use in assisted reproductive technology (ART) for freezing and thawing of pronuclear oocytes and cleavage-stage embryos, respectively.

2.2 Indication(s) and target population(s)

FreezeKit Cleave: Solutions for freezing of pronuclear oocytes and cleavage-stage embryos.

ThawKit Cleave: Solutions for thawing of frozen pronuclear oocytes and cleavage-stage embryos.

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

2.3 Contraindications and/or limitations

FreezeKit Cleave and ThawKit Cleave contain gentamicin. Do not use in patients with known hypersensitivity/allergy to the component. (However, according to the Indications for Use, FreezeKit Cleave/ThawKit Cleave do not have patient contact.)

3 Device description

3.1 Description of the device

FreezeKit Cleave and ThawKit Cleave are MOPS-buffered media intended to support freezing and thawing of pronuclear oocytes and cleavage-stage embryos, respectively. Based on their Indications for Use, FreezeKit Cleave/ThawKit Cleave will have contact with embryos.

The devices are sterile filtered using aseptic technique. FreezeKit Cleave/ThawKit Cleave are stable until the expiry date shown on the bottle 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 FreezeKit Cleave and ThawKit Cleave include gentamicin and human serum albumin (HSA). Gentamicin, an antibiotic, may cause sensitization or allergic reactions in the patient or user.

Figure 1. FreezeKit Cleave/ThawKit Cleave

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

There have been no previous versions of FreezeKit Cleave and ThawKit Cleave 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, 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 Indications for Use, FreezeKit Cleave/ThawKit Cleave do 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 devices according to their IFUs. A benefit-risk analysis concluded that the benefits of including HSA in FreezeKit Cleave and ThawKit Cleave 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 have been reported for any of Vitrolife’s media devices that contain HSA. To mitigate risks, the source material is tested for blood-borne diseases by accredited laboratories. Raw materials for FreezeKit Cleave/ThawKit Cleave are quality tested, and each LOT of the final product is tested for pH, osmolality, sterility, embryo toxicity and bacterial endotoxins. Additionally, the user is informed about the device components, contraindications, warnings and precautions by providing information on labels and the IFUs.

All the clinical risks that could occur during the use of FreezeKit Cleave/ThawKit Cleave are presented 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 FreezeKit Cleave are listed.

- Discard product if bottle integrity is compromised. Do not use FreezeKit Cleave if it appears cloudy.
- FreezeKit Cleave 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 risk 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.

Precautions related to the use of ThawKit Cleave are listed.

- Discard product if bottle integrity is compromised. Do not use ThawKit Cleave if it appears cloudy.
- ThawKit Cleave 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 risk 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 FreezeKit Cleave/ThawKit Cleave during their lifecycles.

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 FreezeKit Cleave/ThawKit Cleave. Post-warming survival rates reported after use of FreezeKit Cleave/ThawKit Cleave [1-5] align with the Alpha competency values [6]. Clinical pregnancy rates reported after use of FreezeKit Cleave/ThawKit Cleave [2, 5] align with the European results published ESHRE [7]. Several references reported data on live births after the use of FreezeKit Cleave/ThawKit Cleave [3-5], which supports the safety of the devices. 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 FreezeKit Cleave/ThawKit Cleave. However, results from a PMCF end user survey confirm the safety and performance of FreezeKit Cleave/ThawKit Cleave 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. FreezeKit Cleave/ThawKit Cleave has been on the market since 2012, and no non-serious incidents or undesirable side-effects were identified after the use of FreezeKit Cleave/ThawKit Cleave with a frequency or severity that negatively impacts their benefit-risk profile.

5.4 An overall summary of the clinical performance and safety

According to the Indications for Use, the clinical benefit of FreezeKit Cleave/ThawKit Cleave is as solutions for freezing and thawing of pronuclear oocytes and cleavage-stage embryos. Post-warming survival rates reported after use of FreezeKit Cleave/ThawKit Cleave [2-5] align with the Alpha competency values [6]. Clinical pregnancy rates reported after use of FreezeKit Cleave/ThawKit Cleave align with the yearly European results published by ESHRE [7]. Data from post-market surveillance, including a PMCF end user survey, and risk management also support the safety and performance of FreezeKit Cleave/ThawKit Cleave. There were no indications of any negative effects from the use of FreezeKit Cleave/ThawKit Cleave. As identified in the risk management documents, two residual risks due to HSA are unacceptable. However, after benefit-risk evaluation, the benefits of using HSA in the devices outweigh 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 devices are used according to their 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 FreezeKit Cleave/ThawKit Cleave. However, general PMCF procedures, such as screening of scientific literature and searching adverse event databases will be performed.

6 Possible diagnostic or therapeutic alternatives

ART is a treatment option for patients unable to conceive naturally as well as those 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.

Cryopreservation methods include slow freezing and vitrification. Current evidence indicates that vitrification is superior to slow freezing in terms of cryosurvival rates and clinical outcomes for oocytes and cleavage-stage embryos. Devices with similar intended use as FreezeKit Cleave/ThawKit Cleave are available in the European Union.

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 devices according to their IFUs. As no special design feature or safety concerns were identified for FreezeKit Cleave/ThawKit Cleave, no specific training is required for end-users.

8 Reference to any harmonized standards and common specifications applied

- Medical Devices Regulation (MDR) (EU) 2017/745
- 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	2021/03/17	Initial version of SSCP for FreezeKit Cleave/ThawKit Cleave (REP-3338-v.1.0)	
2	2022/04/03	Annual update of SSCP for FreezeKit Cleave/ThawKit Cleave (REP-3338-v.2.0)	
3	2022/10/04	Address DNV clinical NCs (REP-3338-v.3.0)	☑ Yes Validation language: English

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
4	2023/06/28	Annual update of SSCP for FreezeKit Cleave/ThawKit Cleave (REP-3338-v.4.0)	
5	See publish date	Annual update of SSCP for FreezeKit Cleave/ThawKit Cleave (REP-3338-v.5.0)	☑ Yes Validation language: English

10 References

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2. Fang L, Jin L, Li E, Cui L, Ye Y: Clinical evaluation of two formulations of slow-freezing solutions for cleavage stage embryos. *J Assist Reprod Genet* 2016, 33(10):1389-1393.
3. Capodanno F, Daolio J, De Feo G, Falbo A, Morini D, Nicoli A, Braglia L, Villani M, La Sala GB, Parmegiani L *et al*: A monocentric analysis of the efficacy of extracellular cryoprotectants in unfrozen solutions for cleavage stage embryos. *Reprod Biol Endocrinol* 2019, 17(1):84.
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5. Ye Y, Ma J, Cui L, Lu S, Jin F: A Rapid NGS-Based Preimplantation Genetic Testing for Chromosomal Abnormalities in Day-3 Blastomere Biopsy Allows Embryo Transfer Within the Same Treatment Cycle. *Front Genet* 2021, 12:636370.
6. Alpha Scientists in Reproductive Medicine: The Alpha consensus meeting on cryopreservation key performance indicators and benchmarks: proceedings of an expert meeting. *Reprod Biomed Online* 2012, 25(2):146-167.
7. 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.