

Summary of safety and clinical performance

SpermCryo[®] All-round SpermTec[®] Cryo

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 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.

1 DEVICE IDENTIFICATION AND GENERAL INFORMATION

1.1 Device trade name(s)

- SpermCryo All-round
- SpermTec Cryo

1.2 Manufacturer's name and address

Gynotec B.V.
Jonckherenhof 7
6581 GC Malden
The Netherlands

1.3 Manufacturer's single registration number (SRN)

NL-MF-000020379

1.4 Basic UDI-DI

1.5 Medical device nomenclature description / text

Applicable EMDN code: U08020502 (Materials/solutions for preparation/handling for assisted reproduction)

1.6 Class of device

Class III according to European Medical Device Directive 93/42/ EEC with amendment 2007/47/EC, Annex II.

(Class III according to Annex VIII of the MDR (Regulation (EU) 2017/745))

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

2017

1.8 Authorized representative if applicable; name and the SRN

n.a.

1.9 NB's name (the NB that will validate the SSCP) and the NB's single identification number

DEKRA Certification B.V.

NB single identification number: 0344

2 INTENDED USE OF THE DEVICE

2.1 Intended purpose

SpermCryo and SpermTec Cryo media are cell culture media for the cryopreservation of human spermatozoa. The media are designed to ensure the recovery of sperm suitable for Assisted Reproductive Technologies (ART) upon cryopreservation. SpermCryo and SpermTec Cryo is a more concentrated

cryopreservation medium than most competitive products which allows lower dilution of the sperm samples before freezing.

2.2 Indication(s) and target population(s)

SpermCryo and SpermTec Cryo media are used to store donor and partner spermatozoa before assisted reproduction treatments (e.g. intrauterine insemination (IUI), in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)), to preserve spermatozoa before therapy for malignant diseases, vasectomy or surgical infertility treatments and to ensure the recovery of small number of spermatozoa in severe male factor infertility. Therefore, sperm cryopreservation is an important component of fertility management and is routinely used in ART clinics/andrology labs.

There is no direct patient contact, SpermCryo and SpermTec Cryo media only come in direct physical contact with human spermatozoa.

2.3 Contraindications and/or limitations

There are no known contraindications and/or limitations identified for SpermCryo and SpermTec Cryo media.

3 DEVICE DESCRIPTION

3.1 Description of the device

SpermCryo and SpermTec Cryo media are cell culture media for the cryopreservation of human spermatozoa.

The media are designed to cryopreserve sperm before further use in ART and 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 Gynotec B.V. is approved by the EMA (European Medicine Agency).

SpermCryo and SpermTec Cryo media contains 27% of glycerol.

The device is not intended for single use. Multiple single-procedures can be performed with one bottle of SpermCryo and SpermTec Cryo media. 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).

SpermCryo and SpermTec Cryo media are sterilized using aseptic processing techniques (filtration).

The lifetime for SpermCryo and SpermTec Cryo 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

N.a.

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

No accessories are intended to be used in combination with the device.

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

SpermCryo and SpermTec Cryo 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 only remaining residual risk is the inclusion of HSA in SpermCryo and SpermTec Cryo media. A potential risk associated with HSA 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 and a human sperm survival assay are routinely performed as part of the 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, Alburnorm 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 SpermCryo and SpermTec Cryo 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. Direct physical contact occurs between SpermCryo and SpermTec Cryo media and human gametes or embryos. With embryo transfer and IUI, the media come into direct contact with the uterus mucosal membranes of the patient. The instructions for use / MSDS clearly warn that the media contains human albumin solution and that protective clothing should be worn.

The major benefit of HSA in SpermCryo and SpermTec Cryo 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.

Based on the 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 SpermCryo and SpermTec Cryo media with inclusion of HSA 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 warning:
 - 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 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, even when the product contains gentamicin
- 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 Gynotec B.V. and the competent authority of the Member State in which the user and/or patient is established

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

No field safety corrective actions with regard to SpermCryo and SpermTec Cryo media 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 to investigate:

- Whether clinical data obtained during literature search are consistent with the embryological and clinical ART outcomes described in the benchmark papers from the ESHRE (European Society of Human Reproduction and Embryology) (see tables below) OR
- Whether clinical data obtained during literature search is within the acceptable defined outcomes concerning the different sperm parameters (motility, vitality, DNA fragmentation and fertilization potential) OR
- Whether the results regarding motility and vitality are not be significantly lower than the results from cryopreservation media of competitors

The embryological outcomes must be consistent with the competency limits as reported by the ESHRE Vienna consensus group in 2017 (ESHRE Special Interest Group of Embryology 2017).

The following competency limits concerning embryological outcomes are reported by the expert group:

- ICSI normal fertilization rate: $\geq 65\%$ (lower range: 60%)
- IVF normal fertilization rate: $\geq 60\%$ (lower range: 50%)
- Since multiple factors can have an influence on the embryology outcomes, (ART policy, approach of the clinic, patients characteristics), a value 10% lower than the competency limit is acceptable.

Clinical ART data obtained from IVF centers should be consistent with the clinical outcomes described in the benchmark paper from the ESHRE.

Each year, the ESHRE publishes a peer-reviewed report, which collects, analyses and reports ART data generated in Europe. The most recent report (Wyns et al. 2022) includes data from 1422 institutions in 39 countries, with a total of 1 007 598 treatment cycles (covering the time period from 1 January to 31 December 2018) and is summarized in the table below:

ART in Europe, 2018: results generated from European registries by ESHRE.

In vitro fertilization (IVF):	Intra cytoplasmic sperm injection (ICSI):	Frozen embryo replacement (FER):	Intrauterine insemination (IUI):
Clinical pregnancy rate per aspiration: 26.2% <i>(range: 7.8 - 47.2%)</i>	Clinical pregnancy rate per aspiration: 24.9% <i>(range: 13.8 - 37.3%)</i>	Pregnancy rate per thawing: 34.6% <i>(range: 24.4 - 49.5%)</i>	using husband semen (IUI-H): Delivery rate per cycle: 9.5% <i>(range: 3.3 - 31.6%)</i>
Clinical pregnancy rate per transfer: 35.9% <i>(range: 21.1 - 50.5%)</i>	Clinical pregnancy rate per transfer: 35.8% <i>(range: 14.8 - 58.3%)</i>	Pregnancy rate per transfer: 35.5% <i>(range: 23.4 - 50.4%)</i>	using donor semen (IUI-D): Delivery rate per cycle: 14.9% <i>(range: 3.2 - 31.4%)</i>
Delivery rate per aspiration: 19.0% <i>(range: 6.3 - 27.8%)</i>	Delivery rate per aspiration: 18.5% <i>(range: 8.7 - 31.3%)</i>	Delivery rate per thawing: 25.2% <i>(range: 17.8 - 40.6%)</i>	
Delivery rate per transfer: 26.4% <i>(range: 14.2 - 38.7%)</i>	Delivery rate per transfer: 26.2% <i>(range: 9.3 - 37.3%)</i>	Delivery rate per transfer: 25.7% <i>(range: 17.1 - 41.4%)</i>	

The following acceptable outcomes of the sperm parameters are set (based on results found in the literature):

- a reduction in sperm motility is set on 50-60% after cryopreservation with SpermCryo and SpermTec Cryo media*
- a reduction in sperm vitality is set on 50% after cryopreservation with SpermCryo and SpermTec Cryo media*
- effect on sperm DNA fragmentation is comparable with that of similar devices with identical intended use as SpermCryo and SpermTec Cryo media on the market
- fertilization potential of sperm cryopreserved with SpermCryo and SpermTec Cryo media is comparable with that of fresh sperm

* In case of a comparative study with similar devices with identical intended use as SpermCryo and SpermTec Cryo 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.

There were 65 articles studying the performance of SpermCryo and SpermTec Cryo media. Overall, it can be concluded from these papers that embryological and ART outcomes, when SpermCryo and SpermTec Cryo media are used, are consistent with the clinical outcomes described in the benchmark papers from the ESHRE (Wyns et al. 2022; ESHRE Special Interest Group of Embryology 2017), suggesting a safe and adequate performance of SpermCryo and SpermTec Cryo media. Also the effects on motility, viability, DNA fragmentation and fertilization potential after cryopreservation of sperm with SpermCryo and SpermTec Cryo media are within acceptable limits and comparable with other products on the market.

5.2 Device registries

In addition, ART outcomes of one IVF clinic located in Europe is included in the clinical evaluation report of SpermCryo and SpermTec Cryo media. It could be concluded that the ART outcomes of the IVF clinic using SpermCryo and SpermTec Cryo media, are consistent with the clinical outcomes, as described in the benchmark paper from the ESHRE (European Society of Human Reproduction and Embryology) (Wyns et al. 2022).

5.3 Summary of clinical data from other sources, if applicable

n.a.

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 circumvent these disadvantages is not yet determined. With this in mind, it is important to evaluate the damaging effects after cryopreservation with SpermCryo and SpermTec Cryo 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 SpermCryo and SpermTec Cryo media. It could be concluded that SpermCryo and SpermTec Cryo 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 outcomes (from literature or received from IVF clinic) of procedures in which the SpermCryo and SpermTec Cryo media are used fall within the normal range of published outcomes as reported by the ESHRE
- 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 SpermCryo and SpermTec Cryo 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 post-market clinical follow-up

Post-market clinical follow-up for SpermCryo and SpermTec Cryo media (including PMCF for the HSA component included in SpermCryo and SpermTec Cryo 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 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 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 SpermCryo and SpermTec Cryo 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 (for further reading see reviews: (Sharma et al. 2015) and (Li et al. 2019)). 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

SpermCryo and SpermTec Cryo 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 HARMONISED STANDARDS AND CS APPLIED

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 Density Gradient media:

- MDR 2017/745: European Medical Device Regulation 2017/745 of 5 April 2017.
- ISO 13485:2016/EN ISO13485:2016/ 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.
- (EN) ISO 10993-18:2020 (Amd 1:2022)/EN ISO 10993-18:2020: Biological evaluation of medical devices – Part 18: Chemical characterization of medical device materials within a risk management process

- (EN) ISO 11737-1:2018, A1:2021: Sterilization of health care products - Microbiological methods - Part 1: Determination of a population of microorganisms on products
- 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.
- 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 17665-1:2006: 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.
- 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 rev. 1: 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 derivative 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
01	15-09-2022	Initial version	Not yet Validation language: English
02	20-11-2023	Update 2023	Not submitted for validation, as there were no significant changes that required validation.

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.

10 REFERENCES

- 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.
- Li, Y. X., L. Zhou, M. Q. Lv, P. Ge, Y. C. Liu, and D. X. Zhou. 2019. 'Vitrification and conventional freezing methods in sperm cryopreservation: A systematic review and meta-analysis', Eur J Obstet Gynecol Reprod Biol, 233: 84-92.
- Sharma, R., A. J. Kattoor, J. Ghulmiyyah, and A. Agarwal. 2015. 'Effect of sperm storage and selection techniques on sperm parameters', Syst Biol Reprod Med, 61: 1-12.
- 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.