Summary of safety and clinical performance

SpermFilter® Ready-to-use gradient 80% – 45% SpermTec® G-80 – G-45

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)

- SpermFilter Ready-to-use gradient 45%
- SpermFilter Ready-to-use gradient 80%
- SpermTec G-45
- SpermTec G-80

1.2 Manufacturer's name and address

FertiPro NV
Industriepark Noord 32
8730 Beernem
Belgium

Exclusive distributor:
Gynotec B.V.
Jonckherenhof 7
6581 GC Malden
The Netherlands

1.3 Manufacturer's single registration number (SRN)

FertiPro NV:
BE-MF-0000000313 (for actor role as manufacturer)
BE-PR-000000330 (for procedure pack producer)

Gynotec B.V.:
NL-MF-000020379

1.4 Basic UDI-DI

5411967GYND5P

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 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

BSI Group The Netherlands B.V.

NB single identification number: 2797

2 INTENDED USE OF THE DEVICE

2.1 Intended purpose

SpermFilter and SpermTec 80-45% media is a sperm preparation method for further use in Intra Uterine Insemination (IUI), In Vitro Fertilization (IVF) Intra-Cytoplasmic Sperm Injection (ICSI), and related Assisted Reproductive Technologies (ART).

2.2 Indication(s) and target population(s)

Although seminal plasma helps spermatozoa penetrate cervical mucus, some of its components (e.g. prostaglandins, zinc) are obstacles to the achievement of pregnancy when natural barriers are bypassed in Assisted Reproductive Technologies (ART), such as Intra-Uterine Insemination (IUI), In-Vitro Fertilization (IVF) or Intra-Cytoplasmatic Sperm Injection (ICSI). The separation of human spermatozoa from seminal plasma to yield a final preparation containing a high percentage of morphologically normal and motile cells, free from debris, non-germ cells and dead spermatozoa, is important for clinical practice.

Density gradient centrifugation is a rapid and powerful method for separating motile spermatozoa from other cell types present in human semen (including immotile spermatozoa, debris, contaminating leukocytes and seminal plasma), without causing damage to the gametes.

Density gradient media are used during ART procedures of patients with infertility problems.
Direct physical contact occurs between the media products and human sperm. The products do not come into contact with the human body.

2.3 Contraindications and/or limitations

There are no known contraindications and/or limitations identified for SpermFilter and SpermTec.

3 DEVICE DESCRIPTION

3.1 Description of the device

SpermFilter and SpermTec 80-45% are ready-to-use density gradient systems for semen preparation, and consist of a defined percentage of silane-coated colloidal silica particles suspended in HEPES-buffered EBSS.

SpermFilter and SpermTec 80-45% contain human serum albumin. The inclusion of human serum albumin (which is a medicinal substance derived from human blood plasma) in ART media from FertiPro/Gynotec is approved by the EMA (European Medicine Agency).

SpermFilter and SpermTec 80-45% contain phenol red and gentamicin. The added gentamicin complies with Ph. Eur. Monograph Standard 0331, is EDQM-certified and is approved by the MEB (Medicine Evaluation Board, competent authority the Netherlands).

Density gradient media can be used in combination with IUI, IVF, ICSI and related ART. The devices are not intended for single use. Multiple single-procedures can be performed with one bottle. 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).

SpermFilter and SpermTec 80-45% are sterilized using aseptic processing techniques (filtration).

In use life time for Density Gradient media is < 27 hours.

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

SpermFilter and SpermTec 80-45% are intended to be used with SpermWash or SpermTec Wash (Class III medical devices – Manufactured by FertiPro NV – Exclusive distributor Gynotec B.V.).

4 RISKS AND WARNINGS

4.1 Residual risks and undesirable effects

The only remaining residual risk is the inclusion of HSA in SpermFilter and SpermTec 80-45% media. The inclusion of this medicinal substance derived from human blood plasma in the devices is approved by the EMA. 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, 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 SpermWash and SpermTec Wash 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 SpermWash and SpermTec Wash 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 SpermFilter and SpermTec 80-45% media is clear:

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

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 SpermWash and SpermTec Wash 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 discoloured (if medium contains phenol red), 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
- Products that include gentamicin should not be used on a patient that has a known allergy to gentamicin or similar antibiotics
- 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 SpermFilter and SpermTec 80-45% 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 paper from the ESHRE (European Society of Human Reproduction and Embryology).

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):

- IVF normal fertilization rate: ≥60% (lower range: 50%)
- ICSI normal fertilization rate: ≥65% (lower range: 60%)
- 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.

The clinical **ART data** must be consistent with the clinical outcomes described in the annual peer-reviewed paper from the ESHRE (most recent paper: (Smeenk et al. 2023)):
ART in Europe, 2019: results generated from European registries by ESHRE.
A total of 1 077 813 treatment cycles, involving 160 782 with IVF, 427 980 with ICSI, 335 744 with frozen embryo transfer (FET), 64 089 with preimplantation genetic testing (PGT), 82 373 with egg donation (ED), 546 with IVM of oocytes and 6 299 with FOR (frozen oocyte replacement) were recorded.

In vitro fertilization (IVF):	Intra cytoplasmic sperm injection (ICSI):	Frozen embryo transfer (FET):	Intrauterine insemination(IUI):
Clinical pregnancy rate per aspiration: **27.0%** *(range: 18.4 – 53.1%)*	Clinical pregnancy rate per aspiration: **24.9%** *(range: 16.0 – 46.1%)*	Pregnancy rate per thawing: **36.5%** *(range: 22.5 – 50.1%)*	**using husband semen (IUI-H):**
Clinical pregnancy rate per transfer: **38.1%** *(range: 27.4 – 63.0%)*	Clinical pregnancy rate per transfer: **37.2%** *(range: 26.9 – 52.1%)*	Pregnancy rate per transfer: **37.1%** *(range: 22.5 – 56.0%)*	Delivery rate per cycle: **9.4%** *(range: 1.9 – 23.1%)*
Delivery rate per aspiration: **19.3%** *(range: 23.3 – 29.4%)*	Delivery rate per aspiration: **17.8%** *(range: 10.6 – 28.6%)*	Delivery rate per thawing: **25.8%** *(range: 7.2 – 41.4%)*	**using donor semen (IUI-D):**
Delivery rate per transfer: **27.6%** *(range: 17.9 – 45.9%)*	Delivery rate per transfer: **27.0%** *(range: 12.1 – 39.4%)*	Delivery rate per transfer: **26.2%** *(range: 8.4 – 42.4%)*	Delivery rate per cycle: **14.3%** *(range: 6.5 – 27.9%)*

There were 35 articles retrieved in literature studying the performance of Density Gradient media. It can be concluded from these papers that embryological and ART outcomes when Density Gradient media are used are consistent with the outcomes described in the benchmark papers from the ESHRE (most recent: Smeenk et al. 2023; ESHRE Special Interest Group of Embryology 2017)), suggesting a safe and adequate performance of Density Gradient media. Density Gradient media as such are able to select for highly motile cells with elevated DNA integrity, without being detrimental for fertilization and embryo development.

5.2 Device registries

In addition to the above, ART outcomes of nine IVF clinics located in Europe are included in the clinical evaluation report of Density gradient media (data not publicly available). IVF centers were asked to provide clinical data using Density Gradient media or when ART data is published in national registers, to sign a statement that Density Gradient media were used during their ART procedures during a certain time period. Overall, it could be concluded that the ART outcomes of the IVF centers are consistent or above the national averages of their country or are consistent with the ART outcomes published in the ESHRE paper (Wyns et al. 2021), indicating that Density Gradient media of Gynotec B.V. not interfere with the general ART procedures.

5.3 Summary of clinical data from other sources, if applicable

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

Overall, it can be concluded that Density Gradient media function as stated by the manufacturer. This is established by clinical data (obtained during literature search and from IVF centers using the device). Moreover, there is no evidence from the clinical data, as well as from the registered complains, market/customer feedback and/or vigilance that Density Gradient media are toxic for gametes and embryos, nor that the media have 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 SpermFilter and SpermTec 80-45% (including PMCF for the HSA and gentamicin component included) 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

Good sperm motility and normal sperm morphology are positively related to oocyte fertilization rates in vitro (Kruger et al. 1988).

The WHO manual (6 h edition, 2021) ‘Examination and processing of human semen’ describes different sperm preparation techniques to select motile and morphologically normal spermatozoa from the whole sperm. With respect to density gradients, the WHO manual states: ‘Discontinuous density gradients can be used as an effective and adaptable method to collect high-quality sperm for ART. It can provide a good selection of motile sperm, free from other cell types and debris. It is easier to standardize than the swim-up technique, and thus results are more consistent. This technique is used to recover and prepare spermatozoa for use in IVF and ICSI’.

Devices with similar intended use as Density Gradient media are available on the European Union or international markets.

7 SUGGESTED PROFILE AND TRAINING FOR USERS

SpermFilter and SpermTec 80-45% 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 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: 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.
- 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 derivate incorporated in a medical device or active implantable medical device.
- (EN) ISO 22442-1: 2020: Medical Devices utilizing animal tissues and their derivatives: Part 1: Application of risk management

- (EN) ISO 11737-1:2018, A1:2021: Sterilization of health care products - Microbiological methods - Part 1: Determination of a population of microorganisms on products

9 REVISION HISTORY

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
01	14-09-2022	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.

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.
- Kruger, T. F., A. A. Acosta, K. F. Simmons, R. J. Swanson, J. F. Matta, and S. Oehninger. 1988. 'Predictive value of abnormal sperm morphology in in vitro fertilization', Fertil Steril, 49: 112-7.
- 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 ESHREdagger', Hum Reprod.