Summary of Safety and Clinical Performance

SpermFilter® Stock Solution 100%
SpermFilter® Ready-to-use gradient 45%
SpermFilter® Ready-to-use gradient 80%
SpermTec® G-100
SpermTec® G-45
SpermTec® G-80

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)

Density Gradient media:
SpermFilter® Stock Solution 100%
SpermFilter® Ready-to-use gradient 45%
SpermFilter® Ready-to-use gradient 80%
SpermTec® G-100
SpermTec® G-45
SpermTec® G-80

1.2 Manufacturer's name and address / distributor information

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)

BE-MF-000000313 (for actor role as manufacturer)

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

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

- CE-marking according to Regulation (EU) 2017/745: 08/11/2023

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

Density Gradient media are used as sperm preparation method for intrauterine insemination (IUI), in vitro fertilization (IVF), intra-cytoplasmic sperm injection (ICSI), and related assisted reproductive technologies (ART).

2.2 Indication(s) and intended patient groups

- **Indications for use:** For use during ART procedures of patients and couples undergoing infertility treatments.
- **Intended users:** The intended users are ART professionals (lab technicians, embryologists, or medical doctors).
- **Target patient populations:** The target patient population consists of patients and couples undergoing infertility treatments.

2.3 Contraindications and/or limitations

There are no known contraindications and/or limitations identified for Density Gradient media.

3 Device description

3.1 Description of the device

- For the principle of operation, reference is made to the IFU: FP09 I13_STG100 R01, FP09 I13_STG, FP09 I13_SPF100 and FP09 I13_SPF R01.
- Density Gradient 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).
- Density Gradient media are sterilized using aseptic processing techniques (filtration).
- Density Gradient media are available with gentamicin. The added gentamicin complies with the European Pharmacopoeia monograph 0331, is certified by the European Directorate for the Quality of Medicines & HealthCare (EDQM) and is approved by the Medicine Evaluation Board (competent authority of the Netherlands.
- Density Gradient media consist of silane-coated colloidal silica particles suspended in HEPES-buffered Earle's balanced salt solution. Sil-Select Plus is additionally contains human serum albumin (HSA). The inclusion of HSA in ART media from FertiPro is approved by the European Medicine Agency (EMA).

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

No accessories for Density Gradient media are identified.

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

DDensity Gradient media are to be used with general ART labware and/or media. In addition, Density Gradient media are intended to be used with SpermWash or SpermTec Wash (both manufactured by FertiPro as class III Medical Devices).

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 and gentamicin are taken into account in the risk management file of Density Gradient media in order to determine the benefits/risk ratio.

The only remaining residual risk is the inclusion of HSA in SpermFilter® Ready-to-use gradient 45%, SpermFilter® Ready-to-use gradient 80%, SpermTec® G-45 and SpermTec® G-80. 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 density gradient media is clear:

- pH regulator
- Osmotic regulator
- Stabilizator of cell membrane
- Nutrient and carrier of growth promoting substances (i.e. amino acids, vitamins, fatty acids, hormones, growth factors)
  Scavenger (of for example toxins and waste products from cell metabolism)
- Surfactant (anti-adhesion), thereby facilitating gamete and embryo manipulation

A potential risk associated with human serum albumin 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 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 Density gradient 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, 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 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 SpermFilter® Ready-to-use gradient 45%, SpermFilter® Ready-to-use gradient 80%, SpermTec® G-45 and SpermTec® G-80 is restricted to the sperm preparation 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 SpermFilter® Ready-to-use gradient 45%, SpermFilter® Ready-to-use gradient 80%, SpermTec® G-45 and SpermTec® G-80 with inclusion for human serum albumin for semen preparation 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 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
- Depending on the number of procedures that will be performed on one day, remove the required volume of medium under aseptic conditions in an appropriate sterile recipient. This is in order to avoid multipe openings/warming cycles of the medium. Discard excess (unused) media.
- Keep in its original packaging until day of use

- Aseptic technique should be used to avoid possible contamination, even when the products 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 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 Density Gradient media 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:

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.	ICSI normal fertilization rate: ≥55% IVF normal fertilization rate: ≥50% Blastocyst development rate: ≥30%

- Clinical ART outcomes:

	In vitro fertilization (IVF):	**Intra cytoplasmic sperm injection (ICSI):**	**Frozen embryo transfer (FET):**	**Intrauterine insemination (IUI):**
Smeenk J, Wyns C, De Geyter C, Kupka MS, Bergh C, Cuevas Saiz I, De Neubourg D, Rezabek K, Tandler-Schneider A, Rugescu I, Goossens V. ART in Europe, 2020: results generated from European registries by ESHRE†. Hum Reprod. 2025 Sep 23:deaf179. doi: 10.1093/humrep/deaf179. Epub ahead of print. PMID: 40985526.	Clinical pregnancy rate per aspiration: 6.7 – 36.5% Clinical pregnancy rate per transfer: 23.3 – 48.8% Delivery rate per aspiration: 4.4 – 28.8% Delivery rate per transfer: 14.9 – 43.9%	Clinical pregnancy rate per aspiration: 9.3 – 38.9% Clinical pregnancy rate per transfer: 25.1 – 49.0% Delivery rate per aspiration: 8.0 – 28.2% Delivery rate per transfer: 10.3 – 39.4%	Pregnancy rate per thawing: 21.7 – 52.6% Pregnancy rate per transfer: 22.3 – 54.9% Delivery rate per thawing: 4.8 – 43.4% Delivery rate per transfer: 4.9 – 45.2%	Delivery rate per cycle (using husband semen IUI-H): 2.7 – 19.0% Delivery rate per cycle (using donor semen IUI-D): 8.2 – 20.9%

There were 42 articles retrieved in literature studying the performance of Density gradient media. Due to reasons of confidentiality, these papers are not listed. Note however that all outcomes described in these articles are consistent with the outcomes as described in the benchmark papers.

Overall it can be concluded from these papers that embryological and ART outcomes, when Density gradient media are used, are consistent with the outcomes as 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.

5.2 Device registries

Clinical data on more than 14 000 ART procedures (IVF, ICSI, IUI cycles) is obtained from IVF centers in Europe and Africa that use Density Gradient media. Embryology and ART outcomes of these clinics are consistent with the national averages of their country (if available) and are consistent with 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

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) which demonstrate that ART/embryology outcomes of procedures in which Density Gradient media are used are consistent with published outcomes by the Vienna consensus group and the ESHRE.

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. No infrequent complications or problems were detected.

5.5 Ongoing or planned PMS/PMCF

PMS/PMCF for Density Gradient media (including PMS/PMCF for the HSA and gentamicin component included in some variants of the Density Gradient 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

The WHO manual (6h 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

Density Gradient media are used by ART 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 Density Gradient 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 556-2:2015	Sterilization of medical devices – Requirements for medical devices to be designated 'STERILE' –Requirements for aseptically processed medical devices.
(EN) ISO 20417:2021	Medical devices: information supplied by the manufacturer.
(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 17665-1:2024	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
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.
ISO 13408-1:2023 / EN ISO 13408-1:2024	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 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.**
Ph. Eur. 0255	European Pharmacopoeia monograph 0255 – Human albumin solution

Ph. Eur. 331	European Pharmacopoeia monograph 331 – Gentamicin sulfate

9 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.1	8/11/2022	Initial version	Version A.1 is validated by the Notified Body Validation language: English
A.2	20/11/2023	Update 2023	Not submitted for validation, as there were no significant changes that required validation.
A.3	14/11/2024	Update 2024	Not submitted for validation, as there were no significant changes that required validation.
A.4	06/11/2025	Update 2025	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.