SUMMARY OF SAFETY AND CLINICAL PERFORMANCE

GAIN™ MEDIUM

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)

GAIN™ medium

1.2 Manufacturer's name and address

FertiPro NV
Industriepark Noord 32
8730 Beernem
Belgium

1.3 Manufacturer's single registration number (SRN)

BE-MF-000000313

1.4 Basic UDI-DI

5411967GAIN1SL

1.5 Medical device nomenclature description/text

Applicable EMDN code: U08020503 - Materials/culture media for assisted reproduction

1.6 Class of device

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

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

- CE-marking according to the Council Directive 93/42/EEC: 2012
- CE-marking according to Regulation (EU) 2017/745: 16/03/2022

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 use

GAIN™ medium is a single-step cell culture medium for use with human embryos and gametes. GAIN™ medium can be used in all the below procedures:

- For semen washing and Intra Uterine Insemination (IUI).
- For oocytes handling/incubation in preparation of, or during fertilization by In Vitro Fertilization (IVF) / Intra Cytoplasmatic Sperm Injection (ICSI).
- For embryo culture from day 1 to expanded blastocyst stage.
- For embryo transfer.

2.2 Indication(s) and intended patient groups

- **Indications for use:** For use during assisted reproductive technologies (ART) procedures of patients and couples undergoing infertility treatments.
- **Intended users:** The intended users are ART professionals (lab technicians, embryologists, or medical doctors).

- **Intended patient populations:** The target patient population consists of patients and couples undergoing infertility treatments.

2.3 Contraindications and/or limitations

There are no known contra-indications and/or limitations for GAIN™ medium.

3 Device description

3.1 Description of the device

- For the principle of operation, reference is made to the IFU: FP09 I79 R01.
- GAIN™ medium is 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).
- GAIN™ medium is sterilized using aseptic processing techniques (filtration).
- GAIN™ medium is a ready-to-use bicarbonate-buffered balanced salt solution, supplemented with 10 mg/l gentamicin (medicinal substance) and 3.5g/l human serum albumin (medicinal substance derived from human blood plasma) and phenol red.
  The inclusion of HSA (which is a medicinal substance derived from human blood plasma) in ART media from FertiPro is approved by the European Medicine Agency (EMA).
  The added gentamicin (medicinal substance) complies with Ph. Eur. Monograph Standard 0331, is EDQM-certified and is approved by the Medicines Evaluation Board (MEB, the competent authority of The Netherlands).
- Direct physical contact occurs between the medium and human gametes/embryos. With embryo transfer and IUI, the medium comes into direct contact with the uterus mucosal membranes of the patient.

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

GAIN™ medium Early Stage and GAIN™ medium Blastocyst: both media had the same composition than GAIN™ medium, but a subdivision was made for commercial reasons.

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

No accessories identified.

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

GAIN™ medium is to be used with general ART labware and/or media.

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 assessment report of GAIN™ medium in order to determine the benefits/risk ratio.

The only remaining residual risk is the inclusion of HSA in GAIN™ medium. 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 GAIN™ medium is:

- 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 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 (MEA) is routinely performed as part of the batch release criteria of the HSA (incoming inspection). Furthermore, a MEA as well as a human sperm survival assay (HSSA) are routinely performed as part of the GAIN™ medium batch release.
- Transmission of 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. Direct physical contact occurs between FertiCult IVF media and human gametes or embryos. There is no contact with the human body as these media are not intended for embryo transfer. 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 medium outweighs the risk and the overall residual risk related to the use of GAIN™ medium with inclusion of HSA has been judged acceptable.

Furthermore, following information is provided to the customer:

- Product composition is clearly indicated on the labels and instructions for use
- IFU 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

Attention should be paid to the following warnings and precautions (as described in the IFU):

- Do not use the product if:
  - it becomes discoloured, 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
- Keep in its original packaging until the day of use.
- Product 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 multiple openings/warming cycles of the medium. Discard excess (unused) media.
- Keep away from (sun)light
- Aseptic techniques should be used to avoid possible contamination, even though 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 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 GAIN™ medium was needed so far.

5 Summary of clinical evaluation and post-market clinical follow-up (PMCF)

5.1 Real-world 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:	≥65%
	IVF normal fertilization rate:	≥60%
	Blastocyst development rate:	≥40%

- Clinical ART outcomes:

	IVF	ICSI	FET	IUI
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 ESHRE', Hum Reprod, 38(12): 2321–2338.	Clinical pregnancy rate per aspiration: *18.4 – 53.1%*	Clinical pregnancy rate per aspiration: *16.0 – 46.1%*	Pregnancy rate per thawing: *22.5 – 50.1%*	Using husband semen (IUI-H): Delivery rate per cycle: *1.9 – 23.1%)*
	Clinical pregnancy rate per transfer: *27.4 – 63.0%*	Clinical pregnancy rate per transfer: *26.9 – 52.1%*	Pregnancy rate per transfer: *22.5 – 56.0%*	
	Delivery rate per aspiration: *12.3 – 29.4%*	Delivery rate per aspiration: *10.6 – 28.6%*	Delivery rate per thawing: *7.2 – 41.4%*	Using donor semen (IUI-D): Delivery rate per cycle: *6.5 – 27.9%)*
	Delivery rate per transfer: *17.9 – 45.9%*	Delivery rate per transfer: *12.1 – 39.4%*	Delivery rate per transfer: *8.4 – 42.4%*	

There were 5 articles retrieved in literature. Overall, it can be concluded from these papers that embryological and clinical ART outcomes, when GAIN™ medium is used are consistent with the outcomes described in the benchmark papers.

A reference list to the papers is provided below:

- Al-Obaidy., Manal Taha. 2016. 'Comparison of the effectiveness of long agonist over the antagonist controlled ovarian hyperstimulation protocols in in vitro fertilization.', *World Journal of Pharmaceutical Research*, 5: 1785-96.
- Al - Jeborry, M.M. 2019. 'Comparison of sandwich, conventional antagonist and microdose protocols in poor responders', *Annals of Tropical Medicine & Public Health* 22: S277.
- Abdul-Razzaq, LN., FJ. Mahmood, and KM. Salih. 2021. 'Across Sectional Study of Iraqi Infertile Women to Evaluate ICSI Procedure', *Annals of R.S.C.B.*, 25: 8228 - 39.
- Abdul-Razzaq, LN., KM. Salih, and BJ. Al-Musawi. 2020. 'Evaluation of Total Antioxidant Capacity in Serum and Follicular Fluid of Women Undergoing ICSI and its Association with Implantation Failure', *Medico-legal Update*, 20.
- Abbas, HH., DM. Al - Jarah, HH. Abbas, and AJ. Chiad. 2020. 'Short Agonist and Antagonist Protocols in Normoresponding Patients Undergoing ICSI, a comparative study', *PJMHS*, 14: 1623-31.

5.2 Device registries

Clinical data was collected from 8 IVF clinics worldwide. The total number of cycles are summarized below:

ART procedure	Number of cycles/transfers
Combined procedures	1 417
FET	1 177
IUI	360
ICSI	2 247
IVF	61

Overall, the reported embryological and/or clinical ART outcomes of all IVF clinics using GAIN™ medium are consistent with the outcomes described in the above mentioned benchmark papers.

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 PMS/ PMCF analysis.

5.4 An overall summary of the clinical performance and safety

GAIN™ medium functions as stated by the manufacturer. This is established by clinical data retrieved from literature and IVF centers which demonstrate that embryological outcomes and ART-outcomes of procedures in which GAIN™ medium was used are consistent with the published outcomes as reported by the Vienna consensus group and the ESHRE.

Furthermore, there is no evidence from the clinical data, as well as from the registered complains, market/customer feedback and/or vigilance that GAIN™ medium is toxic for gametes and embryos, nor that the medium has 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 GAIN™ medium (including PMS/PMCF for the HSA and gentamicin component included in GAIN™ medium) 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 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

Devices with similar intended use as GAIN™ medium are available on the European Union or international markets. Besides these media, there are no other alternative treatments that can be used.

7 Suggested profile and training for users

GAIN™ medium is 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 GAIN™ medium:

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.
(EN) ISO 10993-3:2014	Biological evaluation of medical devices -- Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.
(EN) ISO 10993-5:2009	Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity.
ISO 10993-9:2019 / EN ISO 10993-9:2021	Biological evaluation of medical devices -- Part 9: Framework for identification and quantification of potential degradation products.
(EN) ISO 10993-10:2023	Biological evaluation of medical devices -- Part 10: Tests for irritation and skin sensitization.
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.
(EN) ISO 10993-23:2021	Biological evaluation of medical devices – Part 23: Tests for irritation
(EN) ISO 22442-1: 2020	Medical Devices utilizing animal tissues and their derivatives: Part 1: Application of risk management
Ph. Eur. 331	European Pharmacopoeia monograph 331 – Gentamicin sulfate
Ph. Eur. 0255	European Pharmacopoeia monograph 0255 – Human albumin solution

9 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.3	15/07/2021	Implementation remarks BSI during MDR conformity assessment round 2 + update 2021	Version A.3 is validated by the Notified Body Validation language: English
A.4	30/06/2022	Update 2022	Not submitted for validation, as there were no significant changes that required validation.
A.5	26/07/2023	Update 2023	Not submitted for validation, as there were no significant changes that required validation.
A.6	06/06/2024	Update 2024	Not submitted for validation, as there were no significant changes that required validation.

A.7	28/05/2025	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 since the device is for professional use only.