Summary of Safety and Clinical Performance

GAIN medium

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

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

GAIN medium: 2012

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

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

GAIN medium is a mono-culture system designed in such a way that it contains the optimal concentration of each component to result in maximal response. The mode of action is based on the "let the embryo choose" culture principle: i.e. the medium contains all components that an embryo needs during *in vitro* development from day 0 to the expanded blastocyst stage. In addition, each component is available according the needs of the embryo, in order to support embryo development in the best possible way.

Direct physical contact occurs between the medium products and human gametes or embryos. With embryo transfer and IUI, the medium comes into direct contact with the uterus mucosal membranes of the patient.

GAIN medium is 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).

2.3 Contraindications and/or limitations

There are no known contraindications and/or limitations identified for GAIN medium.

3 Device description

3.1 Description of the device

GAIN medium is a ready-to-use cell culture medium for the in vitro culture/handling of human embryos and gametes. GAIN medium can be used for fertilization, and for zygote/embryo culture from oocytes up to the expanded blastocyst stage. In addition, it can be used for embryo transfer. GAIN medium can also be used for semen washing and for IUI.

GAIN medium contains Human Serum Albumin (HSA) and gentamicin. The inclusion of Human Serum Albumin (which is a medicinal substance derived from human blood plasma) in ART media from FertiPro NV is approved by the EMA (European Medicine Agency). 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).

The device is not intended for single use. Multiple single-procedures can be performed with one bottle of GAIN medium. The medium 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).

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

Historically, GAIN medium has been presented and CE-certified as a set of 2 ready-to-use bicarbonate buffered cell culture media for use in human assisted reproductive technology: GAIN medium Early Stage and GAIN medium Blastocyst. Both media had the same composition (the only differences were limited to the colour of the flip-off cap and product label), but subdivision had been made for commercial reasons. In 2018, FertiPro NV has revised its initial marketing strategy to distinguish between GAIN medium Early Stage and GAIN medium Blastocyst, and renamed the media as GAIN medium because of the increasing demand for single-step medium for human embryos and feedback from labs specialized in Assisted Reproductive Technologies (ART).

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

No accessories for GAIN medium are identified.

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

To maintain pH, temperature and osmolality, the medium should be covered with oil (eg. FertiCult™ Mineral Oil of FertiCult High Viscosity Oil, FertiPro NV, Belgium).

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. 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 is routinely performed as part of the batch release criteria of the HSA (incoming inspection). Furthermore, a mouse embryo assay (MEA) as well as a human sperm survival assay (HSSA) are routinely performed as part of the GAIN medium 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. Direct physical contact occurs between GAIN medium and human gametes or embryos. With embryo transfer and IUI, the medium come into direct contact with the uterus mucosal membranes of the patient. The instructions for use / MSDS clearly warn that the medium contains human albumin solution and that protective clothing should be worn.

The major benefit of HSA in GAIN medium is clear:

- Stabilization of the cell membrane of the embryo in the medium
- Inhibition of lipid peroxidation that can be damaging to sperm
- Carrier and source of essential molecules needed by the embryo
- Detoxification by binding waste products from cell metabolism,
- Facilitating gamete/embryo manipulation by preventing adsorption to the surface through saturation of potential binding sites

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.

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, 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
- Keep away from (sun)light
- Do not re-sterilize after opening
- Product 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
- 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 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 embryological or clinical ART obtained during literature search are consistent with the outcomes as described in the benchmark papers from the ESHRE (European Society of Human Reproduction and Embryology) (see tables below).

The Vienna consensus paper is a report of an expert meeting on the development of ART laboratory performance indicators, reported by the ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine: see (ESHRE Special Interest Group of Embryology 2017). The following minimal competency limits concerning embryological outcomes are reported by the expert group:

Minimal competency limits reported by the ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine in 2017. The Vienna consensus: report of an expert meeting on the development of art laboratory performance indicators (ESHRE Special Interest Group of Embryology 2017)	ICSI normal fertilization rate:	≥65%
	IVF normal fertilization rate:	≥60%
	Blastocyst development rate:	≥40%

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 transfer (FET):**	**Intrauterine insemination(IUI):**
A total of 1 007 598 treatment cycles, involving 162 837 with IVF, 400 375 with ICSI, 309 475 with frozen embryo replacement (FER), 48 294 with preimplantation genetic testing (PGT), 80 641 with egg donation (ED), 532 with IVM of oocytes and 5444 with FOR (frozen oocyte replacement) were recorded.	Clinical pregnancy rate per aspiration: **26.2%** *(range: 7.8 – 47.2%)* Clinical pregnancy rate per transfer: **35.9%** *(range: 21.1 – 50.5%)* Delivery rate per aspiration:**19.0%** *(range: 6.3 – 27.8%)* Delivery rate per transfer:**26.4%** *(range: 14.2 – 38.7%)*	Clinical pregnancy rate per aspiration: **24.9%** *(range: 13.8 – 37.3%)* Clinical pregnancy rate per transfer: **35.3%** *(range: 14.8 – 58.3%)* Delivery rate per aspiration:**18.5%** *(range: 8.7 – 31.3%)* Delivery rate per transfer:**26.2%** *(range: 9.3 – 37.3%)*	Pregnancy rate per thawing: **34.6%** *(range: 24.4 – 49.5%)* Pregnancy rate per transfer:**35.5%** *(range: 23.4 – 50.4%)* Delivery rate per thawing: **25.2%** *(range: 17.8 – 40.6%)* Delivery rate per transfer: **25.7%** *(range: 17.1 – 41.4%)*	**using husband semen (IUI-H):** Delivery rate per cycle: **9.5%** *(range: 3.3 – 31.6%)* **using donor semen (IUI-D):** Delivery rate per cycle: **14.9%** *(range: 3.2 – 31.4%)*

There were 5 articles retrieved in literature studying the performance of GAIN medium. Overall, it can be concluded from these papers that embryological and/or ART outcomes, when GAIN medium is used, are consistent with the embryological minimal competency limits or are consistent with the ART outcomes described in the benchmark papers from the ESHRE, suggesting a safe and adequate performance of GAIN medium.

5.2 Device registries

In addition to the above, ART outcomes of four IVF clinics located over the whole world are included in the clinical evaluation report of GAIN medium. The outcomes of the clinics resemble the outcomes of the ESHRE , indicating that GAIN medium of FertiPro NV not interferes with the general ART procedure.

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

It can be concluded that GAIN medium functions as stated by the manufacturer. This is established by clinical data (obtained during literature search) which demonstrate that embryological outcomes of procedures in which GAIN medium is used are consistent with the minimal competency limits reported by the Vienna consensus group (ESHRE Special Interest Group of Embryology 2017) or by ART results from literature which indicate that ART outcomes of procedures in which GAIN medium is used are consistent with the published outcomes as reported by the ESHRE, published in the previous year or the same year of that CER update (most recent report is: (Wyns et al. 2022)). In addition, clinical data from IVF centers over the whole world show that ART outcomes of procedures in

which GAIN medium is used are consistent with the published outcomes as reported by the national average values or are consistent with the ART outcomes published by 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 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. These data further suggest that the benefit risk ratio of GAIN medium remains acceptable.

5.5 Ongoing or planned post-market clinical follow-up

Post-market clinical follow-up for GAIN medium (including PMCF for the HSA and gentamicin component included in GAIN medium) will be performed at least yearly.

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

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 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 applicable common specification(s), harmonized standard(s) or applicable guidance document(s)

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 GAIN medium:

- **MDR 2017/745**: European Medical Device Regulation 2017/745 of 5 April 2017.
- **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.
- **(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.
- **(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 10993-23:2021:** Biological evaluation of medical devices – Part 23: Tests for irritation
- **ISO 13408-1:2008 (Amd 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 13485:2016/EN ISO13485:2016 (Amd 2021)**: Medical devices — Quality management systems — Requirements for regulatory purposes.
- **(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.
- **(EN) ISO 14971:2019**: 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.
  (EN) ISO 20417:2021: Medical devices: information supplied by the manufacturer
- **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 (Amd 2021)**: Sterilization of health care products - Microbiological methods - Part 1: Determination of a population of microorganisms on products
- **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 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.
- **(EN) ISO 22442-1: 2020**: Medical Devices utilizing animal tissues and their derivatives: Part 1: Application of risk management

9 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.1	11/01/2021	Initial version	Date: not yet Validation language: English
A.2	16/06/2021	BSI MDR conformity assessment round 1	Date: not yet Validation language: English
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	Date: 18/10/2022 provided to Notified Body Validation language: English
A.5	26/07/2023	Update 2023	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 devices intended for patients, is not applicable as the devices are for professional use only.

11 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.

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.