Summary of safety and clinical performance G-1 PLUS™

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 intended users or patients.

The following information is intended for users/healthcare professionals.

1 Device Identification and general information

1.1	Device trade name	G-1 PLUS™
1.2	Manufacturer's name and address	Vitrolife Sweden AB, Gustaf Werners gata 2, SE-421 32 Västra Frölunda, Sweden
1.3	Manufacturer's single registration number (SRN)	SE-MF-000002389
1.4	Basic UDI-DI	735002591AACDE
1.5	Medical device nomenclature description/text	A solution that provides a physiological environment for the retrieval, culture, maintenance, transfer, and/or storage of human sperm, harvested oocytes (eggs), and/or resulting embryos associated with the method of in vitro fertilization (IVF). The solution typically contains various combinations of salts, carbohydrates, amino acids, enzymes, hormones, albumin, vitamins, and/or drugs (e.g., antibiotics). This is a single-use device.
1.6	Class of device	Class III
1.7	Year when the first certificate (CE) was issued covering the device	2007
1.8	Authorized representative if applicable; name and SRN	Not applicable
1.9	NB's name (the NB that will validate the SSCP) and the NB's single identification number	DNV Product Assurance AS Veritasveien 1 1363 Høvik Norway Single Identification Number: 2460

2 Intended use of the device

2.1 Intended purpose

G-1 PLUS is a medical device intended for use in Assisted Reproductive Technology (ART) as a medium for culture of embryos from the pronucleate stage to day 2 or day 3.

2.2 Indication (s) and target population (s)

The Indication for use of G-1 PLUS is "medium for culture of embryos from the pronucleate stage to day 2 or day 3". The intended target group is an adult or reproductive-age population that undergoes in vitro fertilization (IVF) treatment or fertility preservation.

2.3 Contraindications and/or limitations

G-1 PLUS contains gentamicin. Do not use in patients with known hypersensitivity/allergy to the component.

3 Device description

3.1 Description of the device

G-1 PLUS is a bicarbonate buffered medium containing human serum albumin (HSA), hyaluronan and gentamicin. The device is intended to provide suitable physiological conditions to support culture of human embryos from pronucleate stage to day 2 or day 3. It is ready to use after equilibration at +37°C and 6% CO_2 atmosphere. Based on the Indication for Use, G-1 PLUS will not have contact with patient.

G-1 PLUS has a shelf life of 21 weeks from the date of manufacture and is stable until the expiry date shown on the container labels and the LOT-specific Certificate of Analysis. The medium is sterile filtered using aseptic technique and is sold in PETG bottles (pre-sterilized using gamma irradiation) and tamper evident seal. G-1 PLUS is sold in 30mL media bottles and can be used for up to two weeks after first opening.

Based on regulatory guidelines, the medicinal components present in G-1 PLUS are gentamicin and human serum albumin (HSA).

Figure 1. Picture of G-1 PLUS

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

Previous version of G-1 PLUS was G-1 PLUS version 3 (G-1 PLUS v.3), which was part of Vitrolife G III Series media. G-1 PLUS v. 3 had penicillin as an antibiotic. In 2007, Vitrolife replaced penicillin G with gentamicin due to the greater longevity of gentamicin. In addition to this change, the current version has lipoic acid as an antioxidant component to protect embryos from free oxygen radicals. The previous version of G-1 PLUS is not sold on the market.

*All the data presented in this document are related to the current version of G-1 PLUS sold on the market, unless otherwise specified.

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

Not applicable.

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

General equipment and sterile non-toxic disposables in the IVF lab including CO_2 incubator, G-RINSE, OVOIL, G-MOPS PLUS/supplemented G-MOPS, G-2 PLUS and EmbryoGlue.

4 Risks and warnings

4.1 Residual risks and undesirable effects

The potential risks that could affect the patient or end user during the clinical use of G-1 PLUS are the following:

Effect	Hazardous situation
Patient	Patient exposed to non-biocompatible product
	Patient exposed to microbial contamination or contaminated media
	Patient exposed to contaminated HSA
	Allergic patient exposed to gentamicin
End user	User exposed to gentamicin
	User exposed to HSA
	User exposed to lipoic acid
	User exposed to contaminated HSA
	Allergic user exposed to gentamicin

For G-1 PLUS, all the risks were acceptable after risk control measures except the risks: patient exposed to contaminated HSA and user exposed to contaminated HSA. These risks have the harm ‘permanent effect on patient: viral infection of patient’ or ‘permanent effect on user: viral infection of user’. HSA is derived from human blood and could theoretically be a vector for various diseases such as hepatitis B, hepatitis C and HIV 1/2. The probability of patient or user being virally infected during IVF treatment is extremely low, yet the risk is considered unacceptable. Systematic literature search conducted during clinical evaluation has not identified any negative effects or infection associated with the use of HSA in IVF media. No undesirable effect of adverse event has been reported for any of the Vitrolife’s media containing HSA. The benefit-risk evaluation performed during risk analysis has concluded that the benefits of using HSA in IVF media are greater than the risks associated with blood-borne contamination, as Vitrolife applies relevant safety measures. The raw material source of HSA used in Vitrolife’s media are tested for blood-borne diseases by accredited laboratories.

To control risks related to the use of G-1 PLUS, all the raw materials are quality tested, and each LOT of the final product is also tested for sterility, bacterial endotoxin and embryo toxicity prior to its release. Biological evaluation conclude that all components are nutrients that are either naturally present in mammalian tissues, or they have been used on patients for an extended period. None of the components in the device are carcinogenic, mutagenic or toxic for reproduction and the primary packaging does not contain any hazardous substances or Substances of Very High Concern (SVHC). All materials have been tested to ensure safety of the device. Stability studies confirm the product properties are maintained during the shelf-life. Additionally, the end user is informed about the device components, contraindications, precautions and the risk of using blood-derived products by providing information on labels and Instruction for Use.

4.2 Warnings and precautions

Contraindications

G-1 PLUS contains gentamicin. Do not use in patients with known hypersensitivity/allergy to the component.

Precautions

- Discard product if bottle integrity is compromised. Do not use G-1 PLUS if it appears cloudy.
- G-1 PLUS contains human serum albumin.
- Caution: All blood products should be treated as potentially infectious. Source material from which this product was derived was found negative when tested for antibodies to HIV, HBc, HCV, and HTLV I/II and non-reactive for HbsAg, HCV RNA and HIV-1 RNA and syphilis. No known test methods can offer assurance that products derived from human blood will not transmit infectious agents.
- To avoid contamination Vitrolife strongly recommends that media should be opened and used only with aseptic technique.
- The risk of reproductive toxicity and developmental toxicity for IVF media, including Vitrolife´s IVF media, have not been determined and are uncertain.
- Any serious incident that has occurred in relation to the device should be reported to the manufacturer and the competent authority of the Member State in which the user and/or patient is established.
- Not for injection.
- Discard the product according to standard clinical practice for medical hazardous waste when the procedure is finished.

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 action has been taken for G-1 PLUS during its lifecycle.

5 Summary of clinical evaluation and post-market clinical follow-up

5.1 Summary of clinical data related to equivalent device, if applicable

Not applicable.

5.2 Summary of clinical data from conducted investigations of the device before the CE-marking, if applicable

There is no clinical investigation conducted for G-1 PLUS before its CE-marking.

5.3 Summary of clinical data from other sources, if applicable

A recent systematic literature search from 2022 has identified publications reporting cleavage rates after the use of G-1 PLUS. The calculation of the cleavage rate is influenced by the timing of observation, oocyte maturity, and cleavage rate varies across different reference groups (e.g., IVF versus ICSI, female age, and ejaculated versus surgically retrieved sperm). In the Alpha survey, the competence values ranged from 80 to 95%, with a benchmark of 90 to 100% [1].The results identified in these studies confirm the claim of G-1 PLUS in supporting embryo culture from the pronucleate stage to day 2 or day3.

Reference*	Cleavage rate
[2]Kadoura, 2022	89.39-97.61
[3]Ping, 2022	81.2-86.9
[4]Tao, 2022	99.29
[5]Wang, 2023	95.0-98.6

Reference*	Cleavage rate
[6]Li, 2024	88-97
[7]Qiu,2024	97.02-98.95
[8]Wang, 2024	97.8-98.7

* Studies with population size < 50 are not included.

Apart from cleavage rate, good-quality embryo rate described in the studies [2-7, 9-14] confirm the claim that G-1 PLUS supports development of good-quality cleavage-stage embryos. Additionally, the optimal result of ART procedures is to achieve a clinical pregnancy and have a live birth. The CPR and LBR/DR from treatment cycles including the use of G-1 PLUS aligned with the yearly European results published ESHRE [15].

No undesirable side-effect, trends or vigilance reports have been identified for G-1 PLUS during its post-market surveillance (PMS). Data from biological evaluation concluded biological safety and biocompatibility of G-1 PLUS.

5.4 An overall summary of the clinical performance and safety

According to the Indication for Use, G-1 PLUS is intended to provide clinical benefit by supporting culture of embryos from pronucleate stage to day 2 or day 3. Based on its use, the first measurable endpoint after the use of G-1 PLUS is cleavage rate or rate of embryo development at day 2 or day 3. For G-1 PLUS, data on cleavage rates and good-quality embryos from treatment cycles including its use confirm its ability to support embryo development and confirms the safety and performance according to the Indication for Use and claims. Publications reporting clinical pregnancy or live birth and/or post-natal results further confirm the safe use of G-1 PLUS. The clinical pregnancy rate after the use of G-1 PLUS align with the yearly European results published by ESHRE. Data from biological evaluation, multicenter evaluation, PMS and risk management also add support to the safety and performance of G-1 PLUS. No undesirable side-effects have been identified for G-1 PLUS during its lifecycle and the benefit-risk profile is acceptable. Together, these data confirm safety and performance of G-1 PLUS for its Indication for Use and clinical claims.

5.5 Ongoing or planned post-market clinical follow-up

There are no ongoing or planned PMCF studies for G-1 PLUS. There is sufficient clinical evidence confirming the conformity of G-1 PLUS with applicable regulatory requirements. There are no unanswered questions regarding the performance and safety of the device. Risk management has been effective, no further risks have been identified during the clinical evaluation and the benefit-risk profile is acceptable. However, post-market surveillance will continuously monitor the device during its time on the market and general PMCF procedures will be performed to identify any emerging risks, complications, or performance issues.

6 Possible diagnostic or therapeutic alternatives

ART is a treatment option for patients failing to conceive naturally as well as patients who have tried other treatments such as medications and surgical procedures without success. Hence, there are no therapeutic alternatives for patients at this stage.

G-1 PLUS is a medium intended for use in ART for culture of human embryos from pronucleate stage to day 2 or day 3, together with G-2 PLUS serving as sequential media. Devices with similar intended uses are available in the European Union or other international markets. Another strategy for culturing embryos is the single-step system. Both sequential and single-step culture systems are widely used in clinics, and, at present, there is no consensus as to which approach is optimal.

It should be determined within individual laboratories as to which medium best suits the procedure. Although culture media have shown to have an impact on embryo development, it is one among perhaps hundreds of factors in the IVF laboratory that might affect the outcome and attention must be given to laboratory and clinical factors with the aim to create a controlled laboratory environment [16].

7 Suggested profile and training for users

The end user (IVF professional) is expected to be trained and qualified within the ART field to understand the Indication for Use of G-1 PLUS. Since no special design feature or safety concerns were identified for G-1 PLUS, there is no specific training required for the end-users.

8 Reference to any harmonised standards and common specifications applied

- Medical Devices Regulation (EU) 2017/745 (MDR)
- EN ISO 14971:2019/A11:2021. Medical Devices. Application of risk management to medical devices. 31 December 2021.
- ISO/TR 20416:2020. Medical devices — Post-market surveillance for manufacturers. July 2020
- EN ISO 20417:2021. Medical devices — Information to be supplied by the manufacturer. December 2021
- MDCG 2020-6 Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies. April 2020
- MDCG 2019-9 Rev.1. Summary of safety and clinical performance. A guide for manufacturers and notified bodies. March 2022

The conformity assessment procedure follows Annex IX in the MDR.

9 Revision history

Version	Date issued	Change Description	Revision validated by the Notified Body
v.1.0	2021-03-24	Initial version of draft SSCP for G-1 PLUS (REP-3354)	
v.2.0	2022-05-01	Annual update of SSCP for G-1 PLUS (REP-3354)	
v.3.0	2022-06-07	Edits based on DNV comments (REP-3354)	☑ Yes Validation language: English
v.4.0	2023-03-17	Annual update in 2023	
v.5.0	2024-11-11	Annual update in 2024	
v.6.0	See publish date	Delete the name and reference to similar devices in Section 6	☑ Yes Validation language: English

10 References

1. ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine, *The Vienna consensus: report of an expert meeting on the development of ART laboratory performance indicators.* Reprod Biomed Online, 2017. **35**(5): p. 494-510.

2. Kadoura, S., M. Alhalabi, and A.H. Nattouf, *Follicular fluid PlGF and IVF/ICSI outcomes among PCOS and normo-ovulatory women using different controlled hyperstimulation protocols: A prospective case-control study.* Ann Med Surg (Lond), 2022. **79**: p. 104096.
3. Ping, P., et al., *Comparison of intracytoplasmic sperm injection (ICSI) outcomes in infertile men with spermatogenic impairment of differing severity.* Asian J Androl, 2022. **24**(3): p. 299-304.
4. Tao, P., et al., *Effect of sequential versus single-step culture medium on IVF treatments, including embryo and clinical outcomes: a prospective randomized study.* Archives of Gynecology and Obstetrics, 2022. **305**(3): p. 757-765.
5. Wang, M., et al., *Does smooth endoplasmic reticulum aggregation in oocytes impact the chromosome aneuploidy of the subsequent embryos? A propensity score matching study.* Journal of Ovarian Research, 2023. **16**(1): p. 59.
6. Li, Y., et al., *Usable blastocysts developed from in-vitro-matured metaphase I oocytes in preimplantation genetic testing cycles.* Reproductive BioMedicine Online, 2024. **48**(3): p. 103571.
7. Qiu, F., et al., *Fertilization, pregnancy, and neonatal outcomes after IVF, rescue ICSI, and ICSI in unexplained infertility: A retrospective study.* Molecular Reproduction and Development, 2024. **91**(2): p. e23734.
8. Wang, M., et al., *An overview of CFTR mutation profiles and assisted reproductive technology outcomes in Chinese patients with congenital obstructive azoospermia.* Journal of Assisted Reproduction and Genetics, 2024. **41**(2): p. 505-513.
9. Dong, Y.Q., et al., *In vitro maturation of human oocytes maintaining good development potential for rescue intracytoplasmic sperm injection with fresh sperm.* World J Clin Cases, 2022. **10**(7): p. 2166-2173.
10. Mustapha, H., et al., *Effect of intrauterine administration of human chorionic gonadotropin one day before fresh blastocyst transfer on clinical outcomes: a quasi-experimental study.* Pan Afr Med J, 2022. **42**: p. 27.
11. Zheng, X., et al., *In vitro maturation without gonadotropins versus in vitro fertilization with hyperstimulation in women with polycystic ovary syndrome: a non-inferiority randomized controlled trial.* Hum Reprod, 2022. **37**(2): p. 242-253.
12. Liu, Y., et al., *Controlled ovarian hyperstimulation parameters are not associated with de novo chromosomal abnormality rates and clinical pregnancy outcomes in preimplantation genetic testing.* Frontiers in Endocrinology, 2023. **13**: p. 1080843.
13. Wu, S., et al., *Effects of chromosomal translocation characteristics on fertilization and blastocyst development—a retrospective cohort study.* BMC Medical Genomics, 2023. **16**(1): p. 273.
14. Zhang, X., et al., *Embryo development and live birth resulted from artificial oocyte activation after microdissection testicular sperm extraction with ICSI in patients with non-obstructive azoospermia.* Front Endocrinol (Lausanne), 2023. **14**: p. 1123541.
15. Smeenk, J., et al., *ART in Europe, 2019: results generated from European registries by ESHRE.* Hum Reprod, 2023. **38**(12): p. 2321-2338.
16. Cairo Consensus Group, *'There is only one thing that is truly important in an IVF laboratory: everything' Cairo Consensus Guidelines on IVF Culture Conditions.* Reprod Biomed Online, 2020. **40**(1): p. 33-60.

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