Summary of safety and clinical performance G-2 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-2 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	735002591AADDG
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 2460

2 Intended use of the device

2.1 Intended purpose

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

2.2 Indication (s) and target population (s)

The Indication for use of G-2 PLUS is "medium for culture of embryos from day 3 to the blastocyst stage". 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-2 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-2 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 day 3 to the blastocyst stage. It is ready to use after equilibration at +37°C and 6% CO_2 atmosphere. Based on the Indication for Use, G-2 PLUS will not have contact with patient. However, the IFU of the device states that embryo transfer should be performed in EmbryoGlue® or G-2 PLUS.

G-2 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). G-2 PLUS is sold in 30 mL media bottles and can be used for up to two weeks after first opening.

As per regulatory guidelines, the medicinal components present in G-2 PLUS are gentamicin and human serum albumin (HSA).

Figure 1. Picture of G-2 PLUS

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

The previous version of G-2 PLUS, version 3 (G-2 PLUS v.3), was part of the Vitrolife G III Series media and contained penicillin as an antibiotic. In 2007, Vitrolife replaced penicillin G with gentamicin due to its longer stability. G-2 PLUS v.3 is no longer available on the market.

**All data presented in this document pertain to the current version of G-2 PLUS available on the market, unless otherwise specified.*

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

None.

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 CO2 incubator, heating stage, OVOIL, G-MOPS PLUS/supplemented G-MOPS 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-2 PLUS are the following.

Effect	Hazardous situation
Patient	Patient exposed to gentamicin
	Patient exposed to HSA
	Patient exposed to non-biocompatible product
	Patient exposed to high level of endotoxins
	Patient exposed to microbial contamination or contaminated media
	Patient exposed to contaminated HSA
	Patient exposed to contaminated media or high level of endotoxins
	Patient exposed to unintended product
	Allergic patient exposed to gentamicin
End user	User exposed to gentamicin
	User exposed to HSA
	User exposed to contaminated HSA
	Allergic user exposed to gentamicin

For G-2 PLUS, all risks were acceptable after implementing risk control measures, except for the following: “patient exposed to contaminated HAS” and “user exposed to contaminated HAS”. 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 plasma and, if contaminated, could theoretically be a vector for various diseases such as hepatitis B, hepatitis C and HIV 1/2. While the probability of viral infection during IVF treatment is extremely low, the risk is still considered unacceptable.

A systematic literature review conducted during the clinical evaluation has not identified any negative effects or infections associated with the use of HSA in IVF media. Additionally, no undesirable effects or adverse events have been reported for any of Vitrolife’s media containing HSA. The benefit-risk evaluation performed during risk analysis concluded that the benefits of using HSA in IVF media are greater than the risks associated with blood-borne contamination, as Vitrolife applies strict safety measures. The raw material source of HSA used in Vitrolife’s media is tested for blood-borne diseases by accredited laboratories. To control risks related to the use of G-2 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 concluded 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 of the device. 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-2 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-2 PLUS if it appears cloudy.
- G-2 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-2 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-2 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 several publications reporting blastocyst development rates from treatment cycles including the use of G-2 PLUS for culture of embryos from day 3 to the blastocyst stage. In the Alpha survey, the competence value for blastocyst development rate on Day 5 ranged from 25 to 60% [1]. The results identified in these studies confirm the claim of G-2 PLUS in supporting culture of embryos from day 3 to blastocyst stage.

Reference	Blastocyst development/ formation rate	Calculation
[2] Tao, 2022	63.66	Not described
[3] Wang, 2023	66.3-70.5	No. of blastocysts/ No. of day 3 embryos for extended culture × 100%
[4] Wu, 2023	58-62	No. of blastocysts/ No. of blastocysts cultured × 100%
[5] Chu, 2024	59.9-62.0	No. of blastocysts / No. of cultured embryos for blastocyst formation × 100 %
[6] Li,2024	41-66	No. of blastocysts/ No. of 2PN embryos × 100%
[7] Shi, 2024	11.9-34.4*	No. of blastocysts/ No. of embryos performing blastocyst cultivation × 100%
[8] Wang, 2024	59.9-64.7	No. of blastocysts/ No. of day 3 embryos for extended culture × 100%
[9] Zhao, 2024	87.86-94.32	No. of blastocysts/ No. of cleavage embryos cultured on day 3 × 100%
[10] Zhu, 2024	51.1-53.3	Not described

* In reference Shi, 2024, ICSI was performed on in vitro matured oocytes.

Apart from blastocyst formation rates, rate of good quality embryos (i.e., the proportion of good quality blastocysts on Day 5), available/utilized blastocysts or euploid blastocysts were reported in some studies. Given that there exist different confounding variables for grading blastocyst morphology, no KPI has been recommended to assess the blastocyst quality [1]. Good-quality blastocyst rates described in the studies [2, 5, 11-13] confirm the claim that G-2 PLUS supports development of good-quality blastocysts.

No undesirable side-effect, trends or vigilance reports have been identified for G-2 PLUS during its post-market surveillance (PMS). Data from biological evaluation concluded biological safety and biocompatibility of G-2 PLUS.

5.4 An overall summary of the clinical performance and safety

According to the Indication for Use, G-2 PLUS is intended to provide clinical benefit by supporting culture of embryos from day 3 to the blastocyst stage. Based on its use, the first measurable endpoint after the use of G-2 PLUS is blastocyst development rates. Data obtained on this endpoint from treatment cycles including its use is relevant to confirm its safety and performance. For G-2 PLUS, data on blastocyst development rates and good-quality blastocysts from treatment cycles including its use confirm its ability to support blastocyst development and confirm the safety and performance according to the Indication for Use. Publications reporting clinical pregnancy or live birth and/or post-natal results further confirm the safe use of G-2 PLUS. No undesirable side-effects have been identified for G-2 PLUS during its lifecycle and the benefit-risk profile is acceptable.

Together, these data confirm the safety and performance of G-2 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-2 PLUS. There is sufficient clinical evidence confirming the conformity of G-2 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 conducted 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-2 PLUS is a medium intended for use in ART for culture of human embryos from day 3 to the blastocyst stage, together with G-1 PLUS serving as sequential media. Devices with similar intended use 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 methods are widely used in clinics. Currently, there is no consensus on 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 [14].

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-2 PLUS. Since no special design feature or safety concerns were identified for G-2 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	2021-03-18	Initial version of draft SSCP for G-2 PLUS (REP-3357)	
v.2.0	2022-05-09	Annual update of SSCP for G-2 PLUS	
v.3.0	2022-06-07	Edits according to DNV comments	☑ Yes Validation language: English

Version	Date issued	Change description	Revision validated by the Notified Body
v.4.0	2023-03-22	Annual update in 2023	
v.5.0	2025-01-28	Annual update in 2024	
v.6.0	See publish date	Edit section 6, and adjust the citation format of the references.	☑ 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. 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.
3. 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.
4. 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.
5. Chu, D. and Y. Fu, *Impact of culture media pre-equilibration methods on embryo development.* Reproductive Biology, 2024. 24(3): p. 100897.
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. Shi, C., et al., *Optimal ICSI timing on immature oocytes for low prognosis patients under the POSEIDON classification.* BMC Pregnancy and Childbirth, 2024. 24(1): p. 1-10.
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. Zhao, H., et al., *The impact of clinical and laboratory parameters on clinical pregnancy and live birth rates in fresh cycles: a retrospective study of 9608 high-quality cleavage-stage embryos.* Journal of Ovarian Research, 2024. 17(1): p. 47.
10. Zhu, Y., et al., *Clinical Pregnancy and Live Birth Outcomes after Intracytoplasmic Injection of Fresh versus Frozen Testicular Sperm.* Andrologia, 2024. 2024(1): p. 3802703.
11. Ciaffaglione, M., et al., *Post-Thaw Day 5 Blastocyst Culture Time Prior to Transfer Does Not Affect Assisted Reproduction Technology (ART) Outcomes in Frozen-Thawed Embryo Transfer Cycles.* J Clin Med, 2022. 11(24).
12. Hao, Y., et al., *Maternal and neonatal outcomes following blastocyst biopsy for PGT in single vitrified-warmed embryo transfer cycles.* Reprod Biomed Online, 2022. 44(1): p. 151-162.
13. Zhao, H., et al., *Increased ammonium in culture medium may promote cellular apoptosis and negatively affect pluripotency of human blastocysts.* Archives of Gynecology and Obstetrics, 2023. 307(2): p. 619-624.
14. 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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