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# Summary of safety and clinical performance G-IVF™ 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-IVF™ 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 | 735002591AAFDL |
| 1.5 | Global Medical Device Nomenclature (GMDN) code | 44046 |
| 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<br>Veritasveien 1, 1363 Høvik, Norway<br>2460 |

## 2 Intended use of the device

### 2.1 Intended purpose

G-IVF PLUS is a medical device intended for use in assisted reproductive technology (ART) as a medium for preparation and handling of gametes and for *in vitro* fertilization.

### 2.2 Indication and target population

The Indication for use of G-IVF PLUS is "medium for culture for preparation and handling of gametes and for *in vitro* fertilization". The intended target group is an adult or reproductive-age population that undergoes *in vitro* fertilization (IVF) treatment.

### 2.3 Contraindications and/or limitations

G-IVF 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-IVF PLUS is a bicarbonate buffered medium consisting of human serum albumin (HSA) and gentamicin. The device is intended to provide suitable physiological conditions for preparation and handling of gametes and for *in vitro* fertilization.

G-IVF PLUS is ready to use after equilibration at +37°C and 6% $CO_2$ atmosphere. The medium is sterile filtered using aseptic technique and is available in 30 mL and 60 mL bottles that can be used for up to two weeks after first opening.

Based on regulatory guidelines, the medicinal components present in G-IVF PLUS include gentamicin and HSA.


Figure 1. G-IVF PLUS in a 60 mL bottle

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

There have been no previous version of G-IVF PLUS on the market.

Variants of G-IVF PLUS are:

G-IVF PLUS 30mL, REF 10134

G-IVF PLUS 60mL, REF 10136

## 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 for the IVF lab including $CO_2$ incubator, centrifuge, G-MOPS PLUS/supplemented G-MOPS and SpermGrad.

# 4 Risks and warnings

## 4.1 Residual risks and undesirable effects

For G-IVF PLUS, there are two residual risks that remain unacceptable after risk control measures. These risks have the hazardous situations 'viral infection of the patient' or 'viral infection of user' and are related to HSA present in the device. HSA is derived from human blood and could theoretically be a vector for various diseases such as hepatitis B (HBs-Ag), hepatitis C (Anti-HSV) and HIV 1/2 (Anti-HIV 1/2). The probability of patient or user being virally infected during IVF treatment is extremely small, 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 have been tested for blood-borne diseases by accredited laboratories.

All the clinical risks that could occur during the use of G-IVF PLUS are presented in below.

| Effect | Hazardous situation |
| --- | --- |
| Patient | • Patient exposed to non-biocompatible product<br>• Patient exposed to contaminated HSA |
| End user | • User exposed to gentamicin<br>• User exposed to HSA<br>• Allergic user exposed to gentamicin<br>• User exposed to contaminated HSA |

No adverse events or undesirable side-effects have been reported for the device during its time on the market. To control risks, raw materials for G-IVF PLUS are quality tested and each LOT of the final product is tested for pH, osmolality, sterility, bacterial endotoxins and embryo toxicity. Additionally, the user is informed about the device components, contraindication, and precautions by providing information on labels and the Instruction for Use.

## 4.2 Warnings and precautions

Precautions related to G-IVF PLUS are listed below

- Discard product if bottle integrity is compromised. Do not use G-IVF PLUS if it appears cloudy.
- G-IVF 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 FSCAs have been taken for G-IVF 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-IVF PLUS before its CE-marking.

### 5.3 Summary of clinical data from other sources, if applicable

Clinical experience data from multi-center evaluation comparing Vitrolife's G5 Series media (include G-IVF supplemented with HSA; identical to G-IVF PLUS) and GIII Series media (includes G-FERT/G-FERT PLUS) were collected previously (Vitrolife's internal data). The evaluation had two parts: sibling study and a main study. Data were collected from clinics validating and comparing G5 Series with the previous version (GIII Series), with totally 1345 patients included (100 in sibling study, 1245 in main study). The devices in the two groups were used according to their Indications for Use.

Results from the Multi-Center Evaluation of Vitrolife Media - G5 Series versus GIII Series (Vitrolife, data on file).

| | Endpoint/ parameter examined | Results, G-IVF version 5 Included (G5 Series) * | Results, G-FERT™ Included (GIII Series) | p-value |
|---|---|---|---|---|
| Sibling study | Fertilization rate, IVF | 64% | 68% | NS |
| | Fertilization rate, ICSI | 72% | 70% | NS |
| | Clinical pregnancy rate | 53% | 40% | NS |
| | Implantation rate | 40% | 45% | NS |
| Main study | Fertilization rate, IVF | 69% | 58% | 0.001 |
| | Fertilization rate, ICSI | 76% | 75% | NS |
| | Blastocyst development | 48% | 42% | NS |
| | Clinical pregnancy rate | 47% | 50% | NS |
| | Implantation rate | 27% | 30% | NS |

Abbreviations: NS, not significant
**Note: G-IVF supplemented with HSA-solution in the G5 Series is identical to current G-IVF PLUS available on the market*

The above data include the use of G-IVF supplemented with HSA-solution in the G5 Series group. The only difference between G-IVF and G-IVF PLUS is related to HSA supplementation and G-IVF supplemented with HSA-solution is identical to G-IVF PLUS. In the sibling study, no significant differences were observed between the two media groups. In the main study, there were significantly more oocytes fertilized with conventional IVF in the G5 group as compared to the GIII group. Results on blastocyst development, clinical pregnancy and implantation showed no significant differences between G5 and GIII Series of Vitrolife's IVF media.

A systematic literature search has identified several publications reporting fertilization rates from treatment cycles including the use of G-IVF PLUS for preparation and handling of gametes and for *in vitro* fertilization. Several key references reported fertilization rates from treatment cycles including the use of G-IVF PLUS. Results from these studies align with the competency values described above and confirmed the safety and performance of the device according to its Indication for Use.

| Reference | Fertilization rate |
| --- | --- |
| (Dong et al. 2022) | 61.5-64.7 |
| (Kadoura et al. 2022) | 63.55 – 69-18 |
| (Meng et al. 2022) | 86.76-94.37 |
| (Popkiss et al. 2022) | 65.7 |
| (Rao et al. 2022) | 69.8-71.1 |
| (Tao et al. 2022) | 75.60 |
| (Esmaeilian et al. 2023) | 87 |
| (Viganò et al. 2023) | 77.7 |
| (Zhang et al. 2023b) | 65.79-78.56 |
| (Vergara et al. 2024) | 88.12 |
| (Hu 2024) | 81.25-83.3 |

The clinical pregnancy rate from treatment cycles including the use of G-IVF PLUS aligned with the yearly European results published by ESHRE (Smeenk et al. 2023).

| Reference | Clinical Pregnancy Rate |
| --- | --- |
| (Kadoura et al. 2022) | 42.1-42.9 |
| (Meng et al. 2022) | 49.18 |
| (Tao et al. 2022) | 45.7 |
| (Mao et al. 2022) | 42.02-55.26 |
| (Gunst et al. 2023) | 34.1-35.4 |
| (Zhang et al. 2023a) | 50-63.5 |
| (Zhang et al. 2023b) | 34.48-43.87 |

In addition to the above studies, the publications by (Popkiss et al. 2022; Caddy et al. 2023) also reported clinical pregnancy rates. However, the outcomes in subgroups with day 2 cleavage-stage embryo transfer (vitrified-warmed) or patients with a history of low fertilization (Popkiss et al. 2022; Caddy et al. 2023) had significantly low clinical pregnancy rates as compared to other subgroups. G-IVF PLUS was used in all the subgroups and the improved outcomes observed in comparison groups indicate that the poor results are likely due to study settings or patient history. Several studies have reported live births and/or postnatal results (Meng et al. 2022; Popkiss et al. 2022; Rao et al. 2022; Tao et al.

2022; van Duijn et al. 2022; Caddy et al. 2023) with a total of 7231 children born after the use of G-IVF PLUS.

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

### 5.4 An overall summary of the clinical performance and safety

According to the Indication for Use, the clinical benefit of G-IVF PLUS is to support preparation and handling of gametes and for *in vitro* fertilization. Based on its use, the first measurable endpoint after the use of G-IVF PLUS is fertilization rate. Data obtained on this endpoint from treatment cycles including its use is relevant to confirm its safety and performance. For G-IVF PLUS, there is sufficient clinical evidence confirming its safety and performance. Fertilization rates from treatment cycles including the use of G-IVF PLUS for preparation and handling of oocytes or sperm and in vitro fertilization align with the competency values described in the consensus report for key performance indicators (ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine 2017). This data also confirms the device's clinical benefit and claims. Publications reporting clinical pregnancy or live birth and/or post-natal results further confirm the safe use of G-IVF PLUS. The clinical pregnancy rate after the use of G-IVF PLUS align with the yearly European results published by the European Society of Human Reproduction and Embryology (ESHRE) (Smeenk et al. 2023). Data from PMS and risk management also support the safety and performance of G-IVF PLUS. There are no indications of any negative effects from use of G-IVF PLUS. The risks associated with the use of the device are considered acceptable when weighed against the benefits. Therefore, the benefit-risk profile is considered to be acceptable according to current knowledge/state of the art.

### 5.5 Ongoing or planned post-market clinical follow-up

There are no ongoing or planned PMCF studies for G-IVF PLUS. However, general PMCF procedures, such as screening of scientific literature and searching adverse event databases and conducting a PMCF end user survey will be performed.

## 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. There are no therapeutic alternatives for patients at this stage.

Today, ART procedures can also be used to collect gametes for fertility preservation. It serves as a proactive approach to safeguard reproductive potential, especially when medical conditions or treatments may impact fertility.

G-IVF PLUS is a medium intended for use in ART for culture for preparation and handling of gametes and for *in vitro* fertilization. Devices with similar intended uses as G-IVF PLUS are available in the European Union or other international markets.

## 7 Suggested profile and training for users

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

# 8 Reference to any harmonized standards and common specifications applied

- Medical Devices Regulation (EU) 2017/745 (MDR)
- EN ISO 13485:2016. Medical devices — Quality management systems — Requirements for regulatory purposes
- EN ISO 14971:2019. Medical devices — Application of risk management to medical devices
- EN ISO 15223-1:2016. Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements
- EN ISO 20417:2021. Medical devices — Information to be supplied by the manufacturer MEDDEV 2.7/4
- EN ISO/TR 20416:2020. Medical devices — Post-market surveillance for manufacturers
- 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 will be performed according to the procedure outlined in Annex IX of the MDR (EU) 2017/745.

# 9 Revision history

| SSCP revision number | Date issued | Change description | Revision validated by the Notified Body |
|---|---|---|---|
| 1 | 2021/03/18 | Initial version of draft SSCP for G-IVF PLUS (REP-3362-v.1.0) | |
| 2 | 2022/04/03 | Annual update of SSCP for G-IVF PLUS (REP-3362-v.2.0) | |
| 3 | 2022/06/07 | Edits according to DNV comments (REP-3362-v.3.0) | |
| 4 | 2023/02/28 | Annual update of SSCP for G-IVF PLUS (REP- 3362-v.4.0) | |
| 5 | 2024/11/07 | Annual update of SSCP for G-IVF PLUS (REP- 3362-v.5.0) | |
| 6 | 2025/03/10 | Edit section 6 of SSCP for G-IVF PLUS (REP- 3362-v.6.0) | ☑ Yes<br>Validation language: English |

# References

Abdala A, Elkhatib I, Bayram A, Arnanz A, El-Damen A, Melado L, Lawrenz B, Coughlan C, Garrido N, Fatemi HM et al. 2021. Euploidy rates are not affected when embryos are cultured in a continuous (CCM) or sequential culture medium (SCM): a sibling oocyte study. *J Assist Reprod Genet* **38**: 2199-2207.

Bodri D, Sugimoto T, Serna JY, Kondo M, Kato R, Kawachiya S, Matsumoto T. 2015. Influence of different oocyte insemination techniques on early and late morphokinetic parameters: retrospective analysis of 500 time-lapse monitored blastocysts. *Fertility and sterility* **104**: 1175-1181.e1171-1172.

Caddy M, Popkiss S, Weston G, Vollenhoven B, Rombauts L, Green M, Zander-Fox D. 2023. PIEZO-ICSI increases fertilization rates compared with conventional ICSI in patients with poor prognosis. *J Assist Reprod Genet* **40**: 389-398.

Cimadomo D, Scarica C, Maggiulli R, Orlando G, Soscia D, Albricci L, Romano S, Sanges F, Ubaldi FM, Rienzi L. 2018. Continuous embryo culture elicits higher blastulation but similar cumulative delivery rates than sequential: a large prospective study. *J Assist Reprod Genet* **35**: 1329-1338.

De Munck N, Santos-Ribeiro S, Mateizel I, Verheyen G. 2015. Reduced blastocyst formation in reduced culture volume. *J Assist Reprod Genet* **32**: 1365-1370.

Dong YQ, Chen CQ, Huang YQ, Liu D, Zhang XQ, Liu FH. 2022. In vitro maturation of human oocytes maintaining good development potential for rescue intracytoplasmic sperm injection with fresh sperm. *World J Clin Cases* **10**: 2166-2173.

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

Esmaeilian Y, Hela F, Bildik G, Akin N, İltumur E, Yusufoglu S, Yildiz CS, Keles İ, Vatansever D, Taskiran C et al. 2023. IVF characteristics and the molecular luteal features of random start IVF cycles are not different from conventional cycles in cancer patients. *Human reproduction* **38**: 113-124.

Gunst J, Vynck M, Hostens K, Standaert V, Roggeman S, Van De Vijver A. 2022. Single vitrified blastocyst transfers using an aseptic microdroplet vitrification-warming system: live birth rate is determined by expansion rate on day 5 and influenced by morphological quality. *Reproductive BioMedicine Online* **45**: e15-e16.

Hu Y-NH, Liang. 2024. Sperm acrosin activity may be a useful factor in choosing between ICSI and IVF for infertile male patients. *Asian Journal of Andrology*.

Kadoura S, Alhalabi M, Nattouf AH. 2022. 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)* **79**: 104096.

Mao Y, Tang N, Luo Y, Yin P, Li L. 2022. Effects of vitrified cryopreservation duration on IVF and neonatal outcomes. *Journal of ovarian research* **15**: 101.

Meng Q, Xu Y, Zheng A, Li H, Ding J, Xu Y, Pu Y, Wang W, Wu H. 2022. Noninvasive embryo evaluation and selection by time-lapse monitoring vs. conventional morphologic assessment in women undergoing in vitro fertilization/intracytoplasmic sperm injection: a single-center randomized controlled study. *Fertility and sterility* **117**: 1203-1212.

Popkiss S, Horta F, Vollenhoven B, Green MP, Zander-Fox D. 2022. Calcium chloride dihydrate supplementation at ICSI improves fertilization and pregnancy rates in patients with previous low fertilization: a retrospective paired treatment cycle study. *J Assist Reprod Genet*.

Rao M, Tang L, Wang L, Chen M, Yan G, Zhao S. 2022. Cumulative live birth rates after IVF/ICSI cycles with sperm prepared by density gradient centrifugation vs. swim-up: a retrospective study using a propensity score-matching analysis. *Reproductive biology and endocrinology : RB&E* **20**: 60.

Smeenk J, Wyns C, De Geyter C, Kupka M, Bergh C, Cuevas Saiz I, De Neubourg D, Rezabek K, Tandler-Schneider A, Rugescu I et al. 2023. ART in Europe, 2019: results generated from European registries by ESHRE. *Human reproduction*.

Tao P, Zhou W, Yan X, Wu R, Cheng L, Ye Y, Wang Z, Li Y. 2022. 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* **305**: 757-765.

van Duijn L, Rousian M, Kramer CS, van Marion ES, Willemsen SP, Speksnijder JP, Laven JSE, Steegers-Theunissen RPM, Baart EB. 2022. The Impact of Culture Medium on Morphokinetics of Cleavage Stage Embryos: An Observational Study. *Reproductive sciences*.

Vergara F, Fernández J, Pedrosa C, Muñoz M, Jerez E, Varón M, Moyano C, Yoldi A, Ponce J. 2024. Comparative study of intracytoplasmic sperm injection using the traditional holding and the oocyte-holding pipette without aspiration. *Zygote*: 1-6.

Viganò P, Reschini M, Ciaffaglione M, Cucè V, Casalechi M, Benaglia L, Vercellini P, Somigliana E. 2023. Conventional IVF performs similarly in women with and without endometriosis. *Journal of Assisted Reproduction and Genetics* **40**: 599-607.

Zhang HL, Zhao LM, Mao JM, Liu DF, Tang WH, Lin HC, Zhang L, Lian Y, Hong K, Jiang H. 2021. Sperm retrieval rates and clinical outcomes for patients with different causes of azoospermia who undergo microdissection testicular sperm extraction-intracytoplasmic sperm injection. *Asian J Androl*.

Zhang J, Yao G, Zhang T, Hu J, Yang G, He J, He Q, Fan H, Bai Y, Sun Y. 2023a. Effect of calcium ionophore (A23187) on embryo development and its safety in PGT cycles.

Zhang X, Li L, Zhang W, Luo Y, Mao Y, Du H, Li L. 2023b. Embryo development and live birth resulted from artificial oocyte activation after microdissection testicular sperm extraction with ICSI in patients with non-obstructive azoospermia. *Frontiers in Endocrinology* **14**: 1123541.