Summary of safety and clinical performance EmbryoGlue™

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 (IFUs) 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	EmbryoGlue
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	735002591AABDC
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	REF 10085 in 2006 REF 10168 in 2019
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

EmbryoGlue is a medical device intended for use in Assisted Reproductive Technology (ART) as a medium for embryo transfer.

2.2 Indication and target population

The Indication for use of EmbryoGlue is "medium for embryo transfer". The target patient population is an adult or reproductive-age population that undergoes *in vitro* fertilization (IVF) treatment.

2.3 Contraindications and/or limitations

EmbryoGlue contains recombinant human albumin (rHA) (produced in yeast) and gentamicin. Do not use in patients with known hypersensitivity/allergy to any of the components.

3 Device description

3.1 Description of the device

EmbryoGlue is a bicarbonate buffered, physiological salt medium containing rHA, hyaluronan and gentamicin. The composition of EmbryoGlue has been developed to support implantation during embryo transfer. It is ready to use after equilibration at +37°C and 6% CO_2 atmosphere. Based on its Indication for Use, EmbryoGlue has patient contact.

EmbryoGlue is available in a 10 mL bottle (REF 10085) and as a patient pack, which contains 5 × 1.5 mL vials (REF 10168) (Figure 1). The device has a shelf life of 24 weeks (REF 10085) or 30 weeks (REF 10168) from the date of manufacture with storage at +2 to +8 °C 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 or polypropylene copolymer vials (pre-sterilized using gamma irradiation). EmbryoGlue 10mL bottles (REF 10085) can be used for up to two weeks after first opening while 1.5mL vials (REF 10168) should not be stored after opening.

Based on regulatory guidelines, the medicinal components present in EmbryoGlue are rHA and gentamicin.

Figure 1. EmbryoGlue in 10mL bottle (left) or 5x1.5 mLvials (right)

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

Previous version of EmbryoGlue was EmbryoGlue version 3, as a part of Vitrolife GIII Series media. EmbryoGlue version 3 had penicillin G as an antibiotic. In 2007, Vitrolife replaced penicillin G with gentamicin due to its longer satability. EmbryoGlue version 3 is no longer available on the market.

Currently, EmbryoGlue is sold in two different volumes*:

- EmbryoGlue 10 mL (REF 10085) – Packed in PETG bottle with tamper evident seal.
- EmbryoGlue 5 × 1.5 mL (REF 10168) – Packed in USP Class VI Micro packaging vial with closure.

**All data presented in this document are related to the current version of EmbryoGlue 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 for the IVF lab.

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 EmbryoGlue are listed as below.

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

For EmbryoGlue, all the risks were acceptable after risk control measures. For risks related to rHA, the benefit-risk analysis has concluded that the benefits of using rHA are greater than the risks associated with potential hypersensitivity. Systematic literature review conducted during clinical evaluation has not identified any case reports on allergic reactions/hypersensitivity associated with the use of rHA in IVF settings. No adverse events and undesirable side-effects have been reported for the device during its lifetime on the market. To control risks related to the use of EmbryoGlue, all the raw materials are ensured by quality control (QC), and each LOT of the final product is also tested by QC for sterility, bacterial endotoxin and embryo toxicity prior to its release to the market. Biological evaluation has concluded the safe use of EmbryoGlue in clinical settings. 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 the 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 by providing information on labels and Instruction for Use.

4.2 Warnings and precautions

Contraindications

EmbryoGlue® contains recombinant human albumin (produced in yeast) and gentamicin. Do not use in patients with known hypersensitivity/allergy to any of the components.

Warnings or precautions related to the use of EmbryoGlue REF 10085, and REF 10168 are listed.

- Discard product if bottle integrity is compromised. Do not use EmbryoGlue if it appears cloudy.
- 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 product according to standard clinical practice for medical hazardous waste when the procedure is finished.
- Federal (US) law restricts this device to sale by or on the order of a physician or practitioner trained in its use (Rx only).

An additional warning or precaution related to the use of EmbryoGlue REF 10168 is listed.

- Re-use may result in microbiological contamination and/or property changes in the product.

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 actions have been taken for EmbryoGlue during its lifetime.

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 EmbryoGlue before its CE-marking.

5.3 Summary of clinical data from other sources, if applicable

A systematic literature search was conducted to identify clinical data on the safety and performance of EmbryoGlue. An overview of CPRs and LBRs including the use of EmbryoGlue reported by scientific literature from 2022 was summarized in Table 1. The CPRs and LBRs from treatment cycles including the use of EmbryoGlue aligned with the yearly European results published by ESHRE [1].

Table 1. Clinical pregnancy rates (CPRs) and live birth rates (LBRs) after the use of EmbryoGlue reported by literature

Reference	CPR (%)	LBR (%)
[2] Arshad, 2022 *	32.4	NR
[3] Matitashvili, 2022 *	47.9	NR
[4] Baccouri, 2022	31	22.38
[5] Stojanovic Gavrilovic, 2022	56.6	NR

Reference	CPR (%)	LBR (%)
[6] Heymann, 2022	47-57.2	39.0-46.8
[7] Kadoura, 2022 *	36.3	NR
[8] Kalleas, 2022 *	42.2	39.2
[9] Reed, 2022	67.4	NR
[10] Sayed, 2022	NR	11.1[#]-20.1
[11] Horiuchi, 2023	31.7	NR
[12] Le, 2023*	53.2	NR
[13] Nakagawa, 2023	47.4	NR
[14] Ferrandiz, 2023 *	34.3	NR
[15] Koch, 2023 *	55.9	47.1
[16] Yan, 2023	39.6	34.2
[17] Bhoi, 2024	69.5	60.6
[18] Mizobe, 2024*	68.8	58.6
[19] Sorak, 2024	42	NR
[20] Lee, 2023	71.4	NR

Note: NR: Not reported. * The clinical outcomes reported in the articles are stratified by groups, and the outcomes are combined if all groups used EmbryoGlue as the embryo transfer medium. [#] The lower LBR/ET was in embryos with nucleation errors.

5.4 An overall summary of the clinical performance and safety

According to the Indication for Use, EmbryoGlue is intended to support implantation following embryo transfer. Since implantation is the first step in the establishment of pregnancy, clinical pregnancy is considered relevant to confirm the safety and performance of EmbryoGlue. The clinical pregnancy rates reported after the use of EmbryoGlue aligns with the yearly European results published by ESHRE.

The high-level clinical evidence available from systematic review and meta-analysis [6, 21-25] indicates that the addition of HA to an embryo transfer medium is clinically beneficial. Bontekoe et al. 2014 [21] evaluated 16 studies and showed improved clinical pregnancy and live birth rates with the use of functional concentrations of hyaluronan as an adherence compound in ART cycles. The meta-analysis by Heymann et al. 2020 [22] evaluated 26 RCTs and found that functional hyaluronan concentrations (0.5mg/ml) in the transfer media improved clinical pregnancy and live birth rates. Tyler et al. 2022 [23] showed that performing ET with hyaluronic acid versus routine care (n = 9, RR 1.457, 95% CI 1.197-1.261, I2 = 46.48%) led to higher clinical pregnancy rates. Heymann et al. 2022 [6] suggested that HA may be valuable in improving the IVF success rate in treatment cycles with autologous oocytes. There is moderate evidence to conclude that the addition of HA to a transfer medium may increase the chance of live birth from 32% to 39%, with an additional live birth for every 14 embryos transferred. HA addition improves clinical pregnancy rates from 42% to 47% and multiple pregnancy rates from 16% to 23%. He et al. 2023 [24] investigated the effectiveness and safety of 36 different therapies for patients with recurrent implantation failure (RIF) and concluded that embryo medium enriched with HA could significantly improve pregnancy outcomes in these patients.

According to recent good practice recommendations from the ESHRE Add-ons working group, the addition of hyaluronic acid to a transfer medium is recommended. Current data indicate that addition of HA as an adherence compound in ET media in IVF treatment increases LBR following fresh transfers, without a significant effect on adverse outcomes. No effect was seen following frozen-thawed ETs. The higher multiple PRs after the use of a HA-supplemented transfer medium should be further investigated [25].

Data from biological evaluation, PMS and risks management also add support to the safety and performance of EmbryoGlue. No undesirable side-effects have been identified for EmbryoGlue during its lifecycle and the benefit-risk profile is acceptable.

Together, these data confirm safety and performance of EmbryoGlue 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 EmbryoGlue. However, PMS will continuously monitor the device throughout its lifetime and general PMCF procedures such as an end user survey, screening of scientific literature and AE databases will be conducted to identify any emerging risks, AEs/Incidents/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. There are no therapeutic alternatives for patients at this stage.

For embryo transfer, Vitrolife has four products with embryo transfer as an intended use: EmbryoGlue, G2 PLUS, G-TL and Gx-TL. EmbryoGlue has a high concentration of hyaluronan with 0.5 mg/mL and the others have a low concentration of hyaluronan of 0.125 mg/mL.

Meta-analysis and systematic reviews indicate that the addition of a high concentration of hyaluronan to embryo transfer medium is clinically beneficial, reporting improved clinical pregnancy and live birth rates with the use of EmbryoGlue. ESHRE Add-ons working group recommend the addition of hyaluronic acid to transfer media based on the current evidence [25].

7 Suggested profile and training for users

The end user (IVF professional) is expected to follow good practice in IVF laboratories (2015) and use the device according to its IFU. As no special design feature or safety concerns were identified for EmbryoGlue, no specific training is required for end-users.

8 Reference to any harmonized 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	Description	Revision validated by the Notified Body
v.1.0	2020-10-13	Initial version of Draft SSCP for EmbryoGlue (REP-2379)	
v.2.0	2021-09-16	Annual update of SSCP for EmbryoGlue (REP-2379)	
v.3.0	2022-06-30	Annual update of SSCP for EmbryoGlue (REP-2379)	
v.4.0	2022-09-07	Edits according to DNV comments (REP-2379)	
v.5.0	2023-03-16	Edits address of DNV in section 1 (REP-2379)	☑ Yes Validation language: English
v.6.0	2023-10-12	Annual update	
v.7.0	2024-09-30	Annual update	
v.8.0	See publish date	Edit section 6 and adjust the citation format	☑ Yes Validation language: English

10 References

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