Summary of safety and clinical performance Gx-TL™

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	Gx-TL™
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	735002591AAQEA
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	2023
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

Gx-TL is a medical device intended for use in assisted reproductive technology (ART) as a medium for culture of embryos from fertilization to blastocyst stage and embryo transfer

2.2 Indication and target population

The Indication for use of Gx-TL is "medium for culture of embryos from fertilization to blastocyst stage and embryo transfer". The intended target group is an adult or reproductive-age population that undergoes *in vitro* fertilization (IVF) treatment.

2.3 Contraindications and/or limitations

Gx-TL contains gentamicin and acetylcysteine. Do not use in patients with known hypersensitivity/allergy to the component.

3 Device description

3.1 Description of the device

Gx-TL is a bicarbonate-buffered medium containing human serum albumin, hyaluronan, gentamicin and a combination of three antioxidants (acetyl-L-carnitine (ALC), N-acetyl-L-cysteine (NAC), α-lipoic acid (ALA)) and is designed to ensure suitable physiological conditions for developing embryos and protection against oxidative damage.

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

Based on regulatory guidelines, the medicinal components present in Gx-TL include N-acetyl-L-cysteine, gentamicin, human serum albumin (HSA).

Figure 1. Gx-TL in a 30 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 Gx-TL on the market.

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

Gx-TL may be used together with oil for covering of embryo culture media. Other products that may be used in ART procedures are sterile pipettes and multi-well dishes

4 Risks and warnings

4.1 Residual risks and undesirable effects

For Gx-TL, there are three 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 Gx-TL are presented in below.

Effect	Hazardous situation
Patient	• Patient exposed to non-biocompatible product • Patient exposed to microbial contamination or contaminated media • Patient exposed to HSA • Patient exposed to high levels of endotoxins • Patient exposed to contaminated media or high level of endotoxins • Patient exposed to unintended product • Patient exposed to contaminated HSA • Patient exposed to gentamicin • Allergic patient exposed to gentamicin • Patient exposed to acetylcarnitine • Patient exposed to acetylcysteine • Patient exposed to lipolic acid
End user	• User exposed to gentamicin • User exposed to HSA • User exposed to acetylcarnitine • User exposed to acetylcysteine • User exposed to lipolic acid • Allergic user exposed to gentamicin • 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 Gx-TL 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 Gx-TL are listed below

- Discard product if bottle integrity is compromised. Do not use Gx-TL if it appears cloudy.
- Gx-TL contains HSA.
- 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 and developmental toxicity for IVF media, including Vitrolife´s IVF media, has not been determined and is 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 Gx-TL 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

a) Comparisons of human embryonic development in culture medium with and without antioxidant supplementation

Identity of the study	Interim analysis of the study performed in Melbourne IVF centers in Australia and registered with Australian New Zealand Clinical Trials Registry (ANZCTR) (ACTRN12618001479291).
Identity of the device	Gx-TL manufactured by Vitrolife
Intended use of the device in the study	Gx-TL was used for culture of embryos from day 1 to day 5 or day 6.
Objective of the study	Investigate whether the combination of antioxidants favour embryo development in human IVF
Study design	Prospective, randomized controlled superiority study
Primary and secondary endpoint (s)	Primary endpoint is percentage implantation rate following embryo transfer. Secondary endpoints are embryo development day 2 to day 6, embryo quality day 3 to day 6, total blastocyst formation (day 5 and 6), utilization rate, clinical pregnancy rate, neonatal outcome.
Inclusion/exclusion criteria for subject selection	Inclusion criteria: Couples with unexplained infertility intending to undergo IVF or ICSI and where there are no medical contraindications to perform the treatment. The couple should have received verbal and written information/consent about the study. Blastocyst culture and fresh transfer of a single blastocyst. Concomitant medications (e.g.; use of any oral antioxidants) will be recorded Exclusion criteria: Previous participation in the study. Use of PGT where all embryos will be frozen Testicular biopsy patients (TESA/TESE) Total freeze and no transfer possible.
Number of enrolled subjects	The target sample size is 1480. At the interim analysis 275 and 276 patients had received an embryo transfer in the control and antioxidants group, respectively.
Study population	Study is conducted in couples undergoing fertility treatment
Summary of study methods	A traditional IVF treatment including ovarian stimulation and oocyte pick-up was performed using the standard methods at the clinic. Sperm cells were selected according to standard laboratory procedures using media with or without antioxidants. Embryos were cultured in Gx-TL or control media (G-TL) from day 1 to day 5 or day 6 in time-lapse systems manufactured by Vitrolife. Single embryo

	transfers were performed, and clinical pregnancy was determined by monitoring foetal heartbeat after 42 days of gestation.
Summary of results	The overall clinical pregnancy rate in the control group and study group (includes Gx-TL) were 35% and 36%, respectively. The clinical pregnancy rate in female patients ≥35 years old was 27% and 33% in the control (205 transfers) and antioxidant (203 transfers) groups, respectively. The study is ongoing and the results will be updated after the completion of the study.
Limitations of the study, if any:	-
Device deficiency or replacements related to safety and/or performance, if any	-

b) Randomized controlled non-inferiority sibling oocyte study comparing blastocyst development in media with and without antioxidants

Identity of the study	Interim analysis of the study was performed in a single center in Japan and registered with UMIN Clinical Trials Registry (UMIN-CTR) (UMIN000034482)
Identity of the device	Gx-TL manufactured by Vitrolife
Intended use of the device in the study	Gx-TL was used for continuous culture of embryos to the blastocyst stage
Objective of the study	Investigate the efficiency of culture system with antioxidants
Study design	Prospective, randomized controlled non-inferiority sibling oocyte study
Primary and secondary endpoint (s)	The primary endpoint of the study is *in vitro* embryo development. Secondary endpoints are fertilization rate, biochemical pregnancy rate, clinical pregnancy rate
Inclusion/exclusion criteria for subject selection	Inclusion criteria: Patients undergoing ART treatment with more than eight oocytes and patients aimed for blastocyst culture until day 5/6 followed by cryopreservation and transfer of a single embryo in a frozen embryo transfer (FET) cycle. Patients should have received verbal and written information and provided informed consent to participation Exclusion criteria: Previous participation in the study Patients with surgically retrieved sperm, requiring split IVF/ICSI or presenting with less than eight oocytes or more than 33 oocytes at pick-up
Number of enrolled subjects	A total of 143 patients were enrolled and oocytes from each patient were randomly allocated in a 1:1 ratio into either the media with antioxidants (study media group) or standard media without antioxidants (control group)
Study population	Study is conducted in patients undergoing ART treatment
Summary of study methods	All the steps were performed using control (standard media) or the study media system (includes Gx-TL). Washed oocytes were inseminated by either standard IVF or ICSI. Following fertilization, embryos were cultured to the blastocyst stage in the time-lapse system using low oxygen. Embryo development and quality was assessed according to Alpha/ESHRE consensus criteria on day 3 and using Gardner Score for blastocysts on day 5 / 6. Blastocysts of acceptable morphological quality were cryopreserved by vitrification and a single blastocyst is warmed and cultured prior to FET. Clinical outcome parameters (positive beta-human chorionic gonadotropin rate, implantation rate by gestational sac and by foetal heartbeat and live birth) will be monitored when all patients have received at least one embryo transfer

Summary of results	Results showed no significant differences between control and study media in terms of embryo development on day 3 (46 % versus 50 %), good quality blastocysts (30% versus 31%), blastocyst formation day 5+6 (44% versus 45%) and embryo utilization rate (34 % versus 36 %). However, numerically higher rates of fertilization, embryo development were observed, and more number of embryos were available for transfer to the patient in the study media group (media containing antioxidants). The study has been terminated and clinical outcome after embryo transfer will be summarized when all patients have received at least one embryo transfer
Limitations of the study, if any:	-
Device deficiency or replacements related to safety and/or performance, if any	-

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 Gx-TL.

Literature search has identified a peer reviewed article including the use of Gx-TL for culture of embryos from fertilization to blastocyst stage (Ueno et al. 2021). The study compared the outcomes between antioxidant supplemented media and standard media and the embryos were cultured in Gx-TL or control media in time-lapse and non-time-lapse incubator. Results on embryo development, blastocyst quality showed no significant difference between the antioxidant group (Gx-TL) and the standard media group. However, results on clinical pregnancy rate and ongoing pregnancy rate showed significantly higher rates in the Gx-TL group that used non-time-lapse incubator. A meeting abstract reported the use of Gx-TL for *in vitro* oocyte maturation (IVM) (Nakadate et al. 2020) (Asama et al. 2023). The use of Gx-TL for IVM is not according to its Indication for Use and Vitrolife will continue monitoring of the device for any purpose outside the scope of its Indication for Use during its post-market phase.

Additionally, clinical experience data from 15 patients who underwent fertility treatment in a hospital in India showed embryo development after the use of Gx-TL.

According to the results from the literature search, no deviation was found in the safety or performance of the device. No post-market clinical follow-up (PMCF) studies have been conducted for Gx-TL. No non-serious incidents or undesirable side-effects were identified after use Gx-TL with a frequency or severity that negatively impact its benefit-risk profile.

5.4 An overall summary of the clinical performance and safety

According to the Indication for Use, the clinical benefit of Gx-TL is to support culture of embryos from fertilization to the blastocyst stage and allowing embryo transfer to the patient, which is supported by data from published scientific literature. The fertilization rates reported after use of Gx-TL (Ueno et al. 2021) align with the ESHRE competency value (ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine 2017).The CPRs reported after use of Gx-TL (Ueno et al. 2021) align with the yearly European results published by ESHRE (Smeenk et al. 2023). Data from post-market surveillance (PMS) and risk management also support the safety and performance of Gx-TL. There are no indications of any negative effects from use of Gx-TL. 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 Gx-TL. 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.

Fertility preservation can serve as a therapeutic alternative for patients undergoing ART, offering a proactive measure to safeguard reproductive potential, particularly in cases where medical conditions or treatments may impact fertility.

Gx-TL is bicarbonate-buffered medium for culture of embryos from fertilization to blastocyst stage and embryo transfer. Gx-TL contains a combination of three antioxidants, and this makes the device unique for its intended purpose. Devices with similar intended uses as Gx-TL 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 Gx-TL. As no special design feature or safety concerns were identified for Gx-TL, 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	2020/10/13	Initial version of draft SSCP for Gx-TL (REP-2364-v.1.0)	
2	2021/06/04	Update due to DNV comments Gx-TL (REP-2364-v.2.0)	
3	2021/11/02	Update of SSCP due to change in sample size in section 5.2 (REP-2364-v.3.0)	
4	2024/06/27	Annual update of SSCP for Gx-TL (REP- 2364-v.4.0)	
5	2025/03/10	Edit section 6 of SSCP for Gx-TL (REP- 2364-v.5.0)	☑ Yes Validation language: English

References

Asama H, Kamibayashi D, Hashizume A, Michikura Y, Otsuki J. 2023. Focusing on the accumulation of chromatin/chromosomes around nucleoli and optimizing the timing of ICSI to facilitate the rescue in vitro maturation of denuded GV stage oocytes. *Journal of Assisted Reproduction and Genetics* **40**: 2557-2564.

Bolton VN, Cutting R, Clarke H, Brison DR. 2014. ACE consensus meeting report: culture systems. *Hum Fertil (Camb)* **17**: 239-251.

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.

Nakadate M, Fujimura Y, Kenmochi C, Kabashima, Y.,, Aaraki Y, Kubo Y, Sato Y. 2020. Evaluation of antioxidant supplements and autologous follicular fluid supplementation in the medium used for in vitro maturation of GV stage oocytes. *Japan Society of Fertilization and Implantation*.

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*.

Ueno S, Ito M, Shimazaki K, Okimura T, Uchiyama K, Yabuuchi A, Kato K. 2021. Comparison of Embryo and Clinical Outcomes in Different Types of Incubator Between Two Different Embryo Culture Systems. *Reproductive sciences*.

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