Summary of safety and clinical performance Gx-MOPS 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	Gx-MOPS 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	735002591AAREC
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-MOPS PLUS is a medical device intended for use in assisted reproductive technology (ART) as a medium for handling and manipulating oocytes and embryos in ambient atmosphere.

2.2 Indication and target population

The Indication for use of Gx-MOPS PLUS is "medium for handling and manipulating oocytes and embryos in ambient atmosphere". 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-MOPS PLUS 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-MOPS PLUS is a 3-(N-morpholino)-propanesulphonic acid (MOPS) buffered medium containing human serum albumin, 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 the oocytes and embryos in ambient atmosphere and protection against oxidative damage.

Gx-MOPS PLUS is ready to use after equilibration at +37°C and ambient atmosphere. The medium is sterile filtered using aseptic technique and is available in 125 ml bottles that can be used for up to two weeks after first opening.

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

Figure 1. Gx-MOPS PLUS in a 125 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-MOPS PLUS 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-MOPS PLUS may be used for dilution of HYASE-10X™. 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-MOPS PLUS, 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). Gx-MOPS PLUS is not intended to have patient contact. 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-MOPS PLUS are presented in below.

Effect	Hazardous situation
Patient	• Patient exposed to non-biocompatible product • Patient exposed to microbial contamination in media • Patient exposed to contaminated human serum albumin (HSA) • Allergic patient exposed to gentamicin
End user	• User exposed to gentamicin • User exposed to human serum albumin (HSA) • User exposed to acetylcarnitine • User exposed to acetylcysteine • User exposed to lipolic acid • Allergic user exposed to gentamicin • User exposed to contaminated human serum albumin (HSA)

All these risks were acceptable after risk control measures. 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 ASP 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-MOPS PLUS are listed below

- Discard product if bottle integrity is compromised. Do not use Gx-MOPS PLUS if it appears cloudy.
- Gx-MOPS PLUS contains human serum albumin and acetylcysteine.
- 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.
- Not for injection.
- Discard the product according to standard clinical practice for medical hazardous waste when the procedure is finished.
- 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.

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-MOPS 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

a. Randomized controlled non-inferiority sibling oocyte study comparing blastocyst development in media with and without antioxidants (REP-2287-v.1.0)

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-MOPS PLUS manufactured by Vitrolife
Intended use of the device in the study	Gx-MOPS PLUS used for washing oocytes, denudation and intracytoplasmic sperm injection (ICSI)
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 8 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 8 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-MOPS PLUS). Washed oocytes were inseminated by either standard IVF or ICSI. Following fertilization, continuous culture to the blastocyst stage was performed 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 fetal 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 fertilization rates (66% versus 71 %), 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-MOPS PLUS.

Literature search has identified a peer reviewed article including the use of Gx-MOPS PLUS(Ueno et al. 2021). The study compared the outcomes between antioxidant supplemented media and standard media and Gx-MOPS PLUS was used for denudation and ICSI. The study also analyzed the results in relation to the type of incubator used (time-lapse or non-time lapse incubator). Results on fertilization, embryo development, blastocyst quality showed no significant difference between the antioxidant group (Gx-MOPS PLUS) and the standard media group. However, results on clinical pregnancy rate and ongoing pregnancy rate showed significantly higher rates in the Gx-MOPS PLUS group that used non-time-lapse incubator. Additionally, clinical experience data from 15 patients who underwent fertility treatment in a hospital in India showed fertilization and embryo development after the use of Gx-MOPS PLUS for handling of oocytes. These results also add support to the device performance according to its Indication for Use. However, the publication by (Ueno et al. 2021) and clinical experience data showed that Gx-MOPS PLUS was used for sperm preparation/handling, a purpose outside the scope of its Indication for Use. Vitrolife will continue monitoring of the device for any purpose outside the scope of its Indication for Use during its post-market phase.

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-MOPS PLUS. No non-serious incidents or undesirable side-effects were identified after use Gx-MOPS PLUS 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-MOPS PLUS is to support handling and manipulation of oocytes and embryos in ambient atmosphere, which is supported by data from published scientific literature. The fertilization rates reported after use of Gx-MOPS PLUS (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-MOPS PLUS (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-MOPS PLUS. There are no indications of any negative effects from use of Gx-

MOPS 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 Gx-MOPS 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. Hence, 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.

Currently available similar device to Gx-MOPS PLUS

Device characteristics	G-MOPS/G-MOPS PLUS	Multipurpose handling medium (MHM)
Description	G-MOPS: support oocyte collection and handling/manipulation of oocyte and embryos in ambient atmosphere G-MOPS PLUS: support handling and manipulation of oocytes and embryos in ambient atmosphere	Multipurpose Handling Medium (MHM) with Gentamicin is dual buffered solution (HEPES and MOPS) that provides a safe and secure environment to maintain viability of gametes and embryos during manipulations under ambient conditions. It is a versatile solution for swim up preparation, sperm washing, oocyte retrieval and rinsing, IUI, ICSI, and embryo transfer
Indication for Use	G-MOPS: Medium for oocyte collection and for handling and manipulating oocytes and embryos in ambient atmosphere. G-MOPS PLUS: Medium for handling and manipulating oocytes and embryos in ambient atmosphere.	Medium for oocyte retrieval during ovarian follicle aspiration procedures (not for flushing ovarian follicles), washing sperm prior to IVF and ICSI fertilization procedures, and for transport of the embryo to the uterus during embryo transfer procedures.
Intended target population	Adult or reproductive-age population, that undergoes IVF treatment or fertility preservation	-
Intended users	IVF professionals	The product should be used by professionals in ART procedures
Medicinal components	G-MOPS: Gentamicin G-MOPS PLUS: Gentamicin and HSA	Getamicin
Shelf-life	G-MOPS: 25 weeks G-MOPS PLUS: 21 weeks	12 months
Patient contact	G-MOPS: patient contact during oocyte collection G-MOPS PLUS: Not intended to have patient contact	-

Studies comparing the outcomes of Gx-MOPS PLUS and G-MOPS PLUS have shown improved results (e.g., fertilization rate) with the use of Gx-MOPS PLUS; but failed to reach significance. Hence, more studies are required to confirm the benefit of Gx-MOPS PLUS over other commercial devices.

G-MOPS/G-MOPS PLUS are also MOPS buffered media intended to support the handling and manipulation of oocytes and embryos in ambient atmosphere. Multipurpose handling medium is a dual-buffered solution of MOPS and 4-(2-hydroxyethyl)-1-piperazineethanesulphonic acid (HEPES) that is used to maintain stable conditions for gametes and embryos during their manipulation under atmospheric conditions. There is a wide variation in commercially available products for handling oocytes or embryos outside the incubator. Both MOPS and HEPES buffers appear to be safe for maintain stable pH outside the incubator(Cairo Consensus Group 2020). There is no clear evidence confirming the benefit of any IVF handling media over the other. It should be determined within individual laboratories as to which medium best suits the procedure.

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-MOPS PLUS. As no special design feature or safety concerns were identified for Gx-MOPS 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 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-MOPS PLUS (REP-2367-v.1.0)	
2	2021/06/03	Update due to DNV comments Gx-MOPS PLUS (REP-2367-v.2.0)	
3	See publish date	Annual update of SSCP for Gx-MOPS PLUS (REP-2367-v.3.0)	□ Yes Validation language: English

References

Cairo Consensus Group. 2020. 'There is only one thing that is truly important in an IVF laboratory: everything' Cairo Consensus Guidelines on IVF Culture Conditions. *Reprod Biomed Online* **40**: 33-60.

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.

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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