SUMMARY OF SAFETY AND CLINICAL PERFORMANCE

Gx-MOPS™ PLUS

This document is intended to provide an updated summary of clinical data and other information about the safety and clinical performance of the medical device Gx-MOPS PLUS.

This document includes information in accordance with the requirements in Article 32 of the Medical Devices Regulation (EU) 2017/745 (MDR) and recommendations in Medical Device Coordination Group (MDCG) 2019-9 guidance document.

Document History:

Version	Description	Date	Sign
v.1.0	Initial version of SSCP for Gx-MOPS PLUS (REP-2367)	2020-10-13	SM
v.2.0	Update of SSCP based on comments from DNV (REP-2367)	See publish date	SM

List of abbreviations:

ALA	Alpha Lipoic Acid
ALC	Acetyl-L-Carnitine
ART	Assisted Reproductive Technology
FET	Frozen Embryo Transfer
HSA	Human Serum Albumin
ICSI	Intracytoplasmic Sperm Injection
IFU	Instruction for Use
IVF	In Vitro Fertilization
MDCG	Medical Device Coordination Group
MDR	Medical Devices Regulation 2017/745
NAC	N-Acetyl-L-Cysteine
PMCF	Post-Market Clinical Follow-up
SSCP	Summary of Safety and Clinical Performance

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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 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, 421 32 Västra Frölunda, Sweden
1.3 **Manufacturer's single registration number (SRN):** SE-MF-000002389
1.4 **Basic UDI-DI:** 735002591AAREC
1.5 **Medical device nomenclature description/text:** Not available
1.6 **Class of device:** Class III
1.7 **Year when the first certificate (CE) was issued covering the device:** Not yet approved
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:** Det Norske Veritas (DNV) Presafe AS and 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 (s) and target population (s)

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 fertility treatment.

2.3 Contraindications and/or limitations

Gx-MOPS PLUS contains gentamicin. 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 (see figure 1) 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. Picture of 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

Not applicable

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 combination with Gx-MOPS PLUS are sterile labware.

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.

The additional potential clinical risks that could occur during the use of Gx-MOPS PLUS are the following:

- Allergic reaction or hypersensitivity in user
- Patient suffers from cytotoxic reaction following use of the product
- Patient suffers from sensitization reaction following use of the product
- Patient suffers from irritation reaction following use of the product
- Patient suffers from material mediated pyrogenicity reaction following use of the product
- Patient suffers from acute systemic toxicity reaction following use of the product

All these risks were acceptable after risk control measures. To control risks related to the use of Gx-MOPS 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 conclude that all components are nutrients that are either naturally present in mammal tissues, or they have been used in the handling or treatment of human cells for an extended period. No materials or substances are listed as harmful. All chemicals, bottles and final products are MEA tested to confirm non-toxicity. Stability studies confirm the product is non-toxic for the entire lifetime. Additionally, the end user is informed about the device components, contraindications, precautions and risk of using blood derived products by providing information on labels and Instruction for Use.

4.2 Warnings and precautions

Contraindications

Gx-MOPS 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 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.

Additional precautions related to the use of the device can be found in the package insert.

4.3 Other relevant aspects of safety, including a summary of any field safety corrective action (FSCA including FSN) if applicable

Not applicable.

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

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

Literature search has identified a peer reviewed article including the use of Gx-MOPS PLUS (Ueno *et al*., 2021). Ueno et al (2021) 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.

In summary, results observed after the use of Gx-MOPS PLUS by Ueno *et al*., 2021 and clinical experience data aligns with data from clinical investigation.

5.4 An overall summary of the clinical performance and safety

Based on the Indication for Use, Gx-MOPS PLUS is intended to provide clinical benefit by supporting handling and manipulation of oocytes and embryos in ambient atmosphere. For Gx-MOPS PLUS, data from clinical investigation and published article reporting rates of fertilization after the use of the device for washing of oocytes, denudation and ICSI confirm the safety and performance of Gx-MOPS PLUS. Results on embryo development, embryo utilization, implantation and pregnancy rate also demonstrate the safety and performance of Gx-MOPS PLUS. The clinical pregnancy rates reported after the use of Gx-MOPS PLUS by Ueno *et al*., 2021 align with the yearly European results published by ESHRE (Wyns

et al., 2020). Additionally, clinical experience/feedback on the use of Gx-MOPS PLUS in fertility procedures adds support to the device safety and performance.

According to the Indication for Use, Gx-MOPS PLUS can also be used for handling and manipulating embryos at ambient atmosphere. Mouse embryos exposed to Gx-MOPS PLUS in ambient atmosphere for 30 minutes showed no negative effects on embryo development. Given that oocytes are more sensitive to variations in pH or temperature than embryos (Pickering *et al*., 1990; Swain, 2010), the data obtained after the use of Gx-MOPS PLUS for oocyte handling and manipulation supports its safety and performance for embryo handling and manipulation.

There are also data indicating that Gx-MOPS PLUS provides protection against oxidative stress. Mouse embryos developed following exposure to Gx-MOPS PLUS in ambient atmosphere for 30 minutes showed a trend for higher blastocyst cell numbers as compared to those exposed to standard media without antioxidants (G-MOPS PLUS). Additionally, the study comparing outcomes after the use of Gx-MOPS PLUS and G-MOPS PLUS showed numerically higher rates of fertilization, embryo development (day 3), utilization rate in the Gx-MOPS PLUS group (section 5.2a). These results together with data from Ueno *et al*., 2021 indicate the potential benefit of antioxidant supplementation in Gx-MOPS PLUS. No undesirable side-effects have been identified from the use of the device. The risks associated with the use of the device are considered acceptable when weighed against the benefits.

Together, these data confirm safety and performance of Gx-MOPS PLUS for its Indication for Use and all clinical claims.

5.5 Ongoing or planned post-market clinical follow-up

There are no unanswered questions regarding the intended purpose or the performance and safety of the device. No further risks have been recognized during the clinical evaluation and the benefit-risk profile is acceptable. However, Gx-MOPS PLUS being a new device, a PMCF activity will be conducted during its post-market phase and clinical feedback from real-world use of the device will be collected.

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.

Gx-MOPS PLUS is a MOPS buffered medium intended for use in ART for handling and manipulation of oocytes and embryos in ambient atmosphere. G-MOPS and G-MOPS PLUS (Vitrolife) and Multipurpose handling medium (FUJIFILM Irvine Scientific) are the similar devices for Gx-MOPS PLUS. Gx-MOPS PLUS contains a combination of three antioxidants, and this makes the device unique for its intended purpose. 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 (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. Since 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 harmonised standards and common specifications applied

Medical Devices Regulation (EU) 2017/745 (MDR)
MEDDEV 2.7.1 Rev.4
EN ISO 14971:2020 (risk management)
EN ISO 14155:2011 (clinical investigation; Good clinical practice, GCP)
EN ISO 15223-1:2016 (symbols to be used with medical device labelling)
EN 1041: 2008 (information supplied by the manufacturer of medical devices)
MEDDEV 2.7/4 (clinical investigation)
MEDDEV 2.12-2 Rev.2 (post-market clinical follow-up)

9. Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
			☐ Yes Validation language:

10. References

Consensus Group, C. (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.

Pickering, S. J., Braude, P. R., Johnson, M. H., Cant, A., & Currie, J. (1990). Transient cooling to room temperature can cause irreversible disruption of the meiotic spindle in the human oocyte. *Fertil Steril, 54*, 102-108.

Swain, J.E. (2010) Optimizing the culture environment in the IVF laboratory: impact of pH and buffer capacity on gamete and embryo quality. *Reprod Biomed Online*, 21, 6-16.

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*.

Wyns, C., Bergh, C., Calhaz-Jorge, C., De Geyter, C., Kupka, M. S., Motrenko, T., Rugescu, I., Smeenk, J., Tandler-Schneider, A., Vidakovic, S., & Goossens, V. (2020). ART in Europe, 2016: results generated from European registries by ESHRE. *Hum Reprod Open, 2020*, hoaa032

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Document reviewed by Hubert Joris, Tony Winslöf
Document approved by Hans Lehmann on 2021/06/02
Document QA approved by Lars Ketilsson on 2021/06/03