Summary of Safety and Clinical Performance

Fertilization Medium

The purpose of this Summary of Safety and Clinical Performance (SSCP) is to offer public access to an updated summary of the main issues concerning the safety and clinical performance of the device. This document does not replace the Instructions of Use (IFU), which is the main document to ensure the safety of the device, and neither is intended to provide diagnostic or therapeutic suggestions to the intended users.

1 Abbreviations

2PN Two Pro-Nuclei
ART Assisted Reproductive Technology
EMA European Medicines Agency
ESHRE European Society of Human Reproduction and Embryology
EU European Union
HAS Human Albumin Solution
HSA Human Serum Albumin
ICSI Intra Cytoplasmatic Sperm Injection
IFU Instructions For Use
IVF In Vitro Fertilization
MDR Medical Device Regulation
MED Medicines Evaluation Board
NB Notified Body
PMCF Post-Market Clinical Follow-up
SRN Single Registration Number for an economic operator
SSCP Summary of Safety and Clinical Performance
UDI-DI Unique Device Identification - Device Identifier

2 Device identification and general information

2.1 Device trade name(s)

- Fertilization Medium

2.2 Manufacturer's name and address

Kitazato Corporation
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Address: 100-10 Yanagishima, Fuji, Shizuoka 416-0932 Japan
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E-mail : ce_registration@kitazato.co.jp

2.3 Manufacturer's single registration number (SRN)

JP-MF-000018374

2.4 Basic UDI-DI

458223146FERHL

2.5 Medical device nomenclature description/text

Applicable EMDN code U08020503: MATERIALS/ CULTURE MEDIA FOR ASSISTED REPRODUCTION

2.6 Class of device

Fertilization Media are considered medical devices Class III according to MDR (Regulation (EU) 2017/745) Annex VIII

2.7 Year when the first certificate (CE) was issued covering the device

Fertilization Medium: 2024

2.8 Authorized representative if applicable; name and the SRN

Biomedical Supply, S.L. (DIBIMED)
3 Jorge Comín
46015 Valencia, Spain
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info@dibimed.com

SRN: SRN ES-AR-000014358

2.9 NB's name and single identification number

BSI Group The Netherlands B.V.
Say Building, John M. Keynesplein 9
1066 EP Amsterdam
The Netherlands

NB identification number: 2797

3 Intended use of the device

3.1 Intended purpose

Fertilization Medium is a ready-to-use medium intended for washing and holding human oocytes during in vitro fertilization procedures, by IVF or ICSI (until 2PN stage).

3.2 Indication(s) and intended patient groups

Fertilization Medium is used during ART procedures of patients with infertility problems. Specifically, the device is indicated for washing and holding oocytes during in vitro fertilization procedures (IVF or ICSI) until reaching 2PN stage.

Direct physical contact only occurs between the media products and human gametes / embryos. There is no contact with the human body as this medium is not intended for embryo transfer.

Fertilization Medium is used in specialized laboratories performing fertilization techniques, including IVF and ICSI. The intended users are medical specialists trained in fertility treatment (laboratory technicians, embryologists, or medical doctors).

3.3 Contraindications and/or limitations

There are no known contraindications and/or limitations identified for Fertilization Medium.

4 Device description

4.1 Description of the device

Fertilization Medium is a ready-to-use bicarbonate buffered medium intended for washing and holding human oocytes during in vitro fertilization procedures, by IVF or ICSI (until 2PN stage). The medium consists of a balanced salt solution supplemented with Human Serum Albumin (HSA), Gentamicin

Sulphate, and carbohydrate energy sources such as glucose, pyruvate, and lactate. The medium is complete and needs no further additives.

The inclusion of HAS (medicinal substance derived from human blood plasma) in ART media from Kitazato is approved by the European Medicine Agency (EMA).

Gentamicin Sulphate added to the media complies with Ph. Eur. Monograph Standard 0331, is EDQM-certified and is approved by the Medicines Evaluation Board (MED, Netherlands' competent authority).

Fertilization Medium is not intended for single use. Multiple single-procedures can be performed with one bottle of medium, which can be used up to 7 days after bottle opening (when sterile conditions are maintained, and the products are stored at 2-8ºC). The media can be used in combination with several assisted reproduction procedures such as IVF, ICSI and related ART.

Fertilization Medium is sterilized (SAL 10^{-3}) using aseptic processing techniques (filtration).

The media needs to be pre-equilibrated in an incubator at 37ºC and 5-6% CO_2.

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

No previous generations of the device have been brought on the EU market by Kitazato Corporation.

4.3 Description of any accessories which are intended to be used in combination with the device

No accessories for Fertilization Medium are identified.

4.4 Description of any other devices and products which are intended to be used in combination with the device

Not applicable, there are no specific devices and products intended to be used in combination with Fertilization Medium besides general ART labware or media.

5 Risks and warnings

5.1 Residual risks and undesirable effects

The inclusion of Human Serum Albumin (HSA) in Fertilization Medium is approved by the EMA. This is the only residual risk associated with the device and concerning the eventual transmission of viral or prion-carried diseases and the batch-to-batch variation. A description of the residual risks and major benefits is shown below:

Residual risks of Human Serum Albumin (HSA)	Major benefits
1. Batch to batch variation The risk may arise due to the inherent variability in donor blood. Consequently, standardization of the procedures remains difficult. Therefore, a mouse embryo assay is routinely performed as part of the batch release criteria of HSA (incoming inspection). 2. Transmission of viral or prion-carried diseases due to the use of human derived protein source.	1. HSA acts as pH and Osmotic regulator. 2. Inhibition of lipid peroxidation that can be damaging to sperm. 3. Detoxification by binding waste products and toxins from cell metabolism. 4. HSA stabilizes cell membranes and acts as carries or nutrients and growth promoting compounds. 5. HSA prevents cell aggregation and adherence to laboratory equipment facilitating gamete and embryo handling and manipulation.

Along 50 years of clinical use, HSA has been manufactured with a pasteurization procedure that has led to an excellent viral safety. Fertilization Medium will only contain Plasbumin-25 or alternatively, Albunorm 25 as a source of albumin, as these products are covered by a valid Plasma Master File, and the EMA has positively evaluated the usefulness, safety, and benefit of the inclusion of these products in Kitazato Corporation ART-media. Although Fertilization Medium undergoes rigorous quality controls, all cell culture media should still be treated as potentially infectious. At this moment, full assurance that products derived from human blood will not transmit infectious agents cannot be granted by any test method. Fertilization Medium is not intended to be in direct contact with users or patients. Nevertheless, the instructions for use / MSDS clearly warn that the medium contains human albumin solution, and that protective clothing should be worn.	

Based on the analysis above it is concluded that the benefit of adding HSA to Fertilization Medium outweighs the risk and that the overall residual risk related to the use of media including HSA has been judged acceptable.

Accordingly, the instructions for use informs the customer about the product composition and contains the following precautions:

- 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-1/-2, HBV, or HCV, and non-reactive for HbsAg. The known test methods cannot guarantee that products derived from human blood will not transmit infectious agents.
- Standard measures to prevent infections resulting from the implementation of medicinal products prepared from human blood or plasma include effective manufacturing steps for the inactivation/removal of viruses. When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

No other known undesirable side-effects are identified.

5.2 Warnings and precautions

Besides the above, attention should be paid to the following warnings and precautions (as described in the instructions for use):

Warnings	Precautions
• Do not re-sterilize. • Do not freeze the product. • Do not use after the expiration date.	• Product should not be used on a patient that has known allergy to gentamicin or similar antibiotics. • Aseptic technique should be used.

• Do not use if packing is damaged or broken. • Do not use if product becomes cloudy or shows evidence of microbial contamination.	• Use sterilized equipment and materials only. • In case of eye or skin contact with Fertilization Medium, immediately flush eye/skin with water. • Observe all federal, state, and local environmental regulations when discarding the product. • The user shall be responsible for any problems caused by incorrect use of the present IFU. • This product is intended to be used by medical specialists trained in fertility treatment. • 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-1/-2, HBV or HCV, and non-reactive for HbsAg. The known test methods cannot guarantee that products derived from human blood will not transmit infectious agents. • Standard measures to prevent infections resulting from the implementation of medicinal products prepared from human blood or plasma include effective manufacturing steps for the inactivation/removal of viruses. When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. • 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.

5.3 Summary of any field safety corrective action (FSCA including FSN) if applicable

No field safety corrective actions with regard to Fertilization Medium were needed.

6 Summary of clinical evaluation and post-market clinical follow-up (PMCF)

6.1 Summary of clinical data related to equivalent device

Kitazato Corporation has performed a clinical evaluation to support Fertilization Medium approvals and registrations. There is sufficient data available from its clinical use to demonstrate safety and performance of the device.

Fertilization Medium is equivalent/similar to the following devices:

- Sydney IVF Fertilization medium (Cook Medical)
- Fertilization Medium (Genea Biomedx (Merck))
- Sequential Culture Media - Fertilization Medium (Kitazato)
- Global for Fertilization / Global Total for Fertilization / Global Total for Fertilization/w HAS / Global Total LP for Fertilization (LifeGlobal)
- Universal IVF Medium / ORIGIO Sequential Fert (Origio)
- Quinn's Advantage Protein Plus Fertilization (HTF) Medium / Quinn's Advantage Fertilization Medium (Sage)
- G-IVF (PLUS) (VitroLife)
- FertiCult IVF Media (FertiPro) Basic UDI-DI: 5411967FECU1SU. The following clinical data was obtained:

6.2 Real-world evidence analysis

To ensure the safety and performance of Kitazato Fertilization Medium, clinical ART data obtained from IVF centers using the device or its equivalent shall be consistent with the clinical outcomes described in the benchmark articles from the European Society of Human Reproduction and Embryology (ESHRE) (ESHRE Special Interest Group of Embryology 2017), (Wyns et al. 2021):

The Vienna consensus report published in 2017 is the result of a 2-day consensus meeting of expert professionals from Sweden, Turkey, UK, Australia, Italy, Spain, Belgium, Austria, Ireland, Canada, USA, and Norway. As a starting point for the discussion, two surveys were organized to collect information on indicators used in IVF laboratories worldwide. During the meeting, the results of the surveys, scientific evidence (where available), and personal clinical experience were integrated into presentations by experts on specific topics. After presentation, each proposed indicator was discussed until consensus was reached within the panel (ESHRE Special Interest Group of Embryology 2017). The following minimal competency limits concerning embryological outcomes were reported by the expert group:

Minimal competency limits reported by the ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine in 2017. The Vienna consensus: report of an expert meeting on the development of art laboratory performance indicators (ESHRE Special Interest Group of Embryology 2017)	ICSI normal fertilization rate:	≥65% (Lower range: 55%)
	IVF normal fertilization rate:	≥60% (Lower range: 50%)
	Since multiple factors can have an influence on the embryology outcomes, a value 10% lower than the competency limit defined by ESHRE is acceptable	

Additionally, the ESHRE annually publishes a peer-reviewed report analysing ART data generated in Europe. The most recent report includes data from 1,382 institutions in 39 countries, with a total of 940,503 treatment cycles (from 1 January to 31 December 2017) (Wyns et al. 2021) which outcomes are summarized in the table below:

	In vitro fertilization (IVF):	**Intra cytoplasmic sperm injection (ICSI):**	**Frozen embryo replacement (FER):**
ART in Europe, 2017: results generated from European registries by ESHRE A total of 940,503 treatment cycles, involving 165,379 with IVF, 391,379 with ICSI, 271,476 with frozen embryo replacement (FER).	Clinical pregnancy rate per aspiration: **28.3%** *(range: 21.0 – 42.3%)* Clinical pregnancy rate per transfer: **36.2%** *(range: 28.4 – 47.1%)* Delivery rate per aspiration: **21.5%** *(range: 10.4 – 40.9%)* Delivery rate per transfer: **27.5%**	Clinical pregnancy rate per aspiration: **26.3%** *(range: 18.4 – 38.2%)* Clinical pregnancy rate per transfer: **35.2%** *(range: 27.4 – 45.1%)* Delivery rate per aspiration: **20.2%** *(range:12.2 – 36.8%)* Delivery rate per transfer: **26.8%** *(range: 17.5 – 37.4%)*	Pregnancy rate per thawing: **34.4%** *(range: 22.0 – 49.1%)* Pregnancy rate per transfer: ***35.3%*** *(range: 23.5 – 51.3%)* Delivery rate per thawing: ***23.3%*** *(range: 3.2 – 37.8%)* Delivery rate per transfer: ***24.3%*** *(range: 3.2 – 38.6%)*

	(range: 11.2 – 41.5%)		
	Since multiple factors can have an influence on the ART outcomes (ART policy, approach of the clinic, patients characteristics), a value within the range of the ESHRE value is acceptable.		

As there are no alternative treatment options that can be used for washing and handling of oocytes during ART procedures, all data included in the ESHRE report are generated using equivalent media or a similar device available on the market. Reported outcomes in the benchmark article can therefore be considered as benchmark data for ART procedures. Nevertheless, when comparing clinical data, one should be aware that:

- ✓ During ART processes, gametes and embryos are in contact with several (other) ART media and undergo a lot of manipulations that all can have an influence on the reported outcomes.
- ✓ Depending on the patient characteristics, different outcomes can be obtained.

Literature searches are performed to investigate whether embryological and/or clinical ART outcomes obtained from articles that used Kitazato Fertilization Medium or its equivalent device are consistent with the embryological competency limits and/or with the clinical ART outcomes described in the benchmark articles from the ESHRE.

There were four scientific articles retrieved from the literature studying the performance of Fertilization Medium's equivalent devices. In all these reports, embryological and clinical ART outcomes when equivalent fertilization media are used, fall within the range of the outcomes described in the benchmark papers from the ESHRE (ESHRE Special Interest Group of Embryology 2017) (Wyns et al. 2021), demonstrating a safe and adequate performance of Fertilization Medium when used for washing and holding human oocytes during IVF or ICSI procedures until 2PN stage, without being detrimental for fertilization and embryo development.

6.3 Device registers

In addition to the above, ART outcomes of three European IVF clinics are included in the clinical evaluation report of Fertilization Medium (data not publicly available). Each clinic was asked to provide clinical data related with the use of equivalent media in ART procedures performed during a certain period. Moreover, two trials were conducted in cooperation with an IVF clinic located in Europe with the aim of comparing equivalent fertilization medium with a commercial standard IVF medium. Retrieved data demonstrated highly comparable fertilization and blastocyst development rates when the equivalent media was compared with control media from a competitor, as well as consistent embryology and ART outcomes with ESHRE benchmark reports.

From the IVF clinics' data and trials' results, it could be concluded that the obtained ART outcomes of all IVF centres are consistent with the ART outcomes published in the ESHRE reports (ESHRE Special Interest Group of Embryology 2017) (Wyns et al. 2021), indicating that Fertilization Medium does not interfere with ART procedures and ensuring its safety and performance when used according to the instructions for use.

6.4 Summary of clinical data from other sources

The clinical evaluation also includes data pertaining to Fertilization Medium verification and validation testing, performance studies, device registries, client feedback and complaints, vigilance, and the state-of-the-art.

There are no field corrective actions, either safety or non-safety related to the clinical use of equivalent fertilization medium since the product was launched on the market. No emerging risks, systematic missuse, off-label use were identified, nor previously unknown side effects and contra-indications.

According to the multiple manuscripts available in the literature, the use of similar products to Fertilization Medium on the market demonstrates its performance and safety. None of the retrieved articles and reported clinical data on the use of equivalent fertilization media reported side-effects, contra-indications, toxicity for gametes or embryos, or risk for mutagenity, oncogenicity, teratogenity, carcinogenity, cytotoxicity, allergenicity and irritancy (for patients and users). Thus, from the literature data it could be concluded that devices with the same intended use as Fertilization Medium are able to wash and hold oocytes during in vitro fertilization procedures (IVF or ICSI) until 2PN stage, without being detrimental for fertilization and embryo development.

Kitazato Corporation has taken all necessary steps to ensure that residual risks associated with the use of Fertilization Medium are reduced as far as possible through application of existing state of the art techniques in the design and manufacture of these medical devices to ensure safe usage. Kitazato Corporation concludes that the overall medical benefits of Fertilization Medium outweigh the possible risks when used according to the intended use.

6.5 An overall summary of the clinical performance and safety

According to the information exposed in the clinical evaluation report, it can be concluded that Fertilization Medium is not harmful for gametes / embryos during fertilization and embryo development, allowing to wash and hold human oocytes during IVF or ICSI procedures until 2PN stage. No problems or complications were detected for Fertilization Medium.

The remaining risks identified in the Risk Assessment or other risks associated with the washing and holding of human oocytes during IVF or ICSI until 2PN stage using fertilization media, cannot be mitigated further, and are considered acceptable when weighed against the benefits to the patient. All harms have been defined with their potential causes of failure and associated mitigation activities. The only considerable residual risk identified is associated with the fact that these media contain a human blood derivative (Human Albumin Solution, HAS).

Based on this analysis it is concluded that the benefit of adding HSA to the media outweighs the risk, and therefore the residual risk of adding HSA is acceptable.

There is sufficient evidence to establish the safety and performance of Fertilization Medium when used in accordance with the IFU. The data are adequate to assess the benefits and risks associated with the subject device, concluding that the benefit-risk profile is acceptable. Therefore, the initial clinical evaluation demonstrates that the available clinical data are sufficient to establish conformity with all applicable General Safety and Performance Requirements (Annex I) of the Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (MDR) and to confirm the safety and performance of Fertilization Medium. The IFU clearly demonstrates safe use of Fertilization Medium and the mandatory medical training ensures all users are fully familiar with all aspects of device use.

Fertilization Medium has been confirmed to be within the current state-of-the-art practice.

6.6 Ongoing or planned post-market clinical follow-up

On a year basis, Kitazato Corporation will perform literature search for Fertilization Medium. Additionally, clinical data retrieved from IVF centers using Fertilization Medium will be evaluated.

This Summary of Safety and Clinical Performance will be updated with data from the post-market clinical follow-up if required, to guarantee that any clinical and/ or safety information described in this summary stays right and complete.

7 Possible diagnostic or therapeutic alternatives

Multiple literature articles demonstrate comparable results among the different fertilization media available on the market, reporting ART outcomes consistent with those published in the ESHRE benchmark report. Besides commercialized fertilization media, there are no alternative treatments for washing and holding human oocytes during in vitro fertilization procedures, by IVF or ICSI (until 2PN stage).

8 Suggested profile and training for users

Fertilization Medium is used in specialized laboratories performing fertilization techniques, including IVF and ICSI. The intended users are medical specialists trained in fertility treatments (laboratory technicians, embryologists, or medical doctors).

9 Reference to any applicable common specification(s), harmonized standard(s) or applicable guidance document(s)

- MDCG 2019-09: Summary of safety and clinical performance. A guide for manufacturers and notified bodies (August 2019, full applicable).
- EN ISO 13408-1:2015. Aseptic processing of health care products – Part 1: general requirements (full applicable)
- EN ISO 13408-2:2018 Aseptic processing of health care products – Part 2: Filtration (full applicable)

10 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
V.1	05/07/2023	Initial version	Date: not yet Validation language: English
V.2.	20/11/2023	Inclusion of literature articles and vigilance data as per BSI review.	Date: 28/02/2024 Validation language: English

11 Summary of the safety and clinical performance for patients

As the device is for professional use only, a summary of the safety and clinical performance of the device intended for patients is not applicable.

12 References

ESHRE Special Interest Group of Embryology, ESHRE. 2017. 'The Vienna consensus: report of an expert meeting on the development of art laboratory performance indicators', Hum Reprod Open, 2017:hox011.

Wyns, C., C. De Geyter, C. Calhaz-Jorge, M. S. Kupka, T. Motrenko, J. Smeenk, C. Bergh, A. TandlerSchneider, I. A. Rugescu, S. Vidakovic, and V. Goossens. 2021. 'ART in Europe, 2017: results generated from European registries by ESHRE', Hum Reprod Open, 2021: hoab026.