Summary of Safety and Clinical Performance

Flushing Buffer

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

ART Assisted Reproductive Technology
CEP Certificate of Suitability
ESHRE European Society of Human Reproduction and Embryology
EU European Union
FER Frozen Embryo Replacement
FSCA Field Safety Corrective Action
FSN Field Safety Notice
ICSI Intra Cytoplasmatic Sperm Injection
IFU Instructions For Use
IVF In Vitro Fertilization
MDR Medical Device Regulation
MEB 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)

- Flushing Buffer

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

458223146ASPHZ

2.5 Medical device nomenclature description/text

Applicable EMDN code U08020502: MATERIALS/SOLUTIONS FOR PREPARATION/HANDLING FOR ASSISTED REPRODUCTION

2.6 Class of device

Flushing Buffer is considered a medical device of Class III according to MDR (Regulation (EU) 2017/745) Annex VIII

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

Flushing Buffer	2024

2.8 Authorized representative if applicable; name and the SRN

Biomedical Supply, S.L. (DIBIMED)
C/ Jorge Comín, 3
Valencia. 46015. 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

Flushing Buffer is a ready-to-use medium used for oocyte aspiration and follicular flushing as part of Assisted Reproductive Technologies (ART) procedures.

3.2 Indication(s) and intended patient groups

Flushing Buffer is used during ART procedures of patients with infertility problems. Specifically, the device is indicated for oocyte aspiration and follicular flushing as part of Assisted Reproductive Technologies (ART) procedures.

Direct physical contact occurs between the medium and human oocytes or ovarian follicles of the patient during oocyte aspiration and follicular flushing.

Flushing Buffer 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 Flushing Buffer.

4 Device description

4.1 Description of the device

Flushing Buffer is a ready-to-use medium used for oocyte aspiration and follicular flushing as part of Assisted Reproductive Technologies (ART) procedures. The medium consists of a balanced salt

solution supplemented with heparin sodium, HEPES and carbohydrate energy sources such as glucose, pyruvate, and lactate. The medium is complete and needs no further additives.

Flushing Buffer includes 2.5 IU/ml heparin sodium to avoid blood clot formation in the tubing during oocyte aspiration or follicular flushing which might block the aspiration needle and/or difficult the identification and isolation of oocytes. The added heparin complies with Ph. Eur. Monograph Standard 0333 and it is EDQM-certified. The inclusion of heparin sodium (medicinal substance of porcine origin) in Flushing Buffer is submitted for approval by the MEB (Medicine Evaluation Board, Netherlands' competent authority).

Flushing Buffer 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).

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

The media needs to be pre-warmed at 37ºC.

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 Flushing Buffer are identified besides general ART labware/media/equipment. It is advice the use of a rubber-free syringe.

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 Flushing Buffer besides general ART labware.

5 Risks and warnings

5.1 Residual risks and undesirable effects

All identified residual risks were reduced to acceptable levels.

Regarding the addition of heparin to Flushing Buffer, the following is considered:

- Although heparin sodium is a medicinal substance that may increase the risk of abdominal bleeding during oocyte aspiration and/or follicular flushing, the residual risk is considered acceptable after applying risk control measures at design, manufacturing, and information for safety (instructions for use) stages.
- Heparin sodium is derived from animal tissue (porcine intestinal mucosa, alternative sources are currently not available). Heparin sodium used in Flushing Buffer is EDQM certified and is manufactured under GMP conditions, being compliant with all requirements for parenteral use in patients with coagulation disorders. Furthermore, porcine intestinal mucosa is not classified by the WHO and ISO 22442-1 as a tissue with detectable infectivity. Furthermore, Flushing Buffer only contains a small amount of heparin sodium (2.5 IU/ml) and the patient is only exposed to the medium for a short time during oocyte retrieval. Therefore, although risk of viral and TSE infection cannot be fully eliminated, the residual risk is considered acceptable.

According to the points described above, the instructions for use inform the customer about the product composition and contains the following precautions:

- Flushing Buffer contains heparin which is derived from porcine intestinal mucosa. The heparin is certified with a Certificate of Suitability (CEP). The animals from which the heparin is derived, are determined “fit for human consumption”.
- All human, organic material should be considered potentially infectious. Always wear protective clothing when handling specimens.

Based on the analysis above it is concluded that the benefit of adding heparin sodium to Flushing Buffer outweighs the risk and the overall residual risk has been reduced to acceptable levels.

No other known undesirable side-effects are identified.

5.2 Warnings and precautions

Attention should be paid to the following warnings and precautions (as described in the instructions for use):

Warnings	Precautions
• Do not use if product becomes cloudy or shows evidence of contamination. • Do not use if packaging is damaged or broken. • In case of eye or skin contact with Flushing Buffer, immediately flush eye/skin with water. • Do not re-sterilize or freeze the product. • Do not use the product after expiration date.	• Aseptic technique should be used to avoid contamination. • Use sterilized equipment and material only. • Avoid multiple opening cycles of the container. Remove required volume under aseptic conditions in an appropriate sterile recipient. • Flushing Buffer contains heparin which is derived from porcine intestinal mucosa. The heparin is certified with a Certificate of Suitability (CEP). The animals from which the heparin is derived, are determined “fit for human consumption”. • All human, organic material should be considered potentially infectious. Always wear protective clothing when handling specimens. • Observe all federal, state and local environmental regulations when discarding the product. • The user shall be responsible for any problems caused by incorrect use or not following the present IFU. • This product is intended to be used by medical specialists trained in fertility treatment. Any serious incident (as defined in European Medical Device Regulation, 2017/745) that has occurred in relation to the device should be reported to Kitazato Corporation and, if applicable, the competent authority of the EU

	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 Flushing Buffer 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 the Flushing Buffer approvals and registrations. There is sufficient data available from its clinical use to demonstrate safety and performance of the device.

Flushing Buffer is equivalent/similar to the following devices:

- Sydney IVF Follicle Flush buffer (Cook Medical)
- Oocyte Retrieval Buffer (Genea Biomedx (Merck))
- Global Collect / Washing mHTF w/HEPES & phenol red (LifeGlobal)
- SynVitro Flush / Flushing Medium (Origio)
- GM501 Flush (Gynemed)
- Modified Ham's F-10 Basal Medium – HEPES (Irvine Scientific)
- ASP (VitroLife)
- FertiCult Aspiration Media (FertiPro) Basic UDI-DI: 5411967ASPI1V4. Following clinical data was obtained:

6.2 Real-world evidence analysis

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 are 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%)
	Blastocyst development rate:	≥40% (Lower range: 30%)
	Since multiple factors can have an influence on the embryology outcomes, (ART policy, approach of the clinic, patients' characteristics), a value 10% lower than the competency limit is acceptable.	

Clinical ART data obtained from IVF centers using the device or its equivalent should be consistent with the clinical outcomes described in the benchmark article from the European Society of Human Reproduction and Embryology (ESHRE) (Wyns et al. 2022).

Each year, the ESHRE publishes a peer-reviewed report, which collects, analyses and reports ART data generated in Europe. The most recent report includes data from 1,422 institutions in 39 countries, with a total of 1,007,598 treatment cycles (from 1 January to 31 December 2018) (Wyns et al. 2022) and is summarized in the table below:

	In vitro fertilization (IVF):	**Intra cytoplasmic sperm injection (ICSI):**	**Frozen embryo replacement (FER):**
ART in Europe, 2018: results generated from European registries by ESHRE A total of 1,007,598 treatment cycles, involving 162,837 with IVF, 400,375 with ICSI, 309,475 with frozen embryo replacement (FER).	Clinical pregnancy rate per aspiration: **26.2%** *(Range: 7.8 – 47.2%)* Clinical pregnancy rate per transfer: **35.9%** *(Range: 21.1 – 50.5%)* Delivery rate per aspiration: **19.0%** *(Range: 6.3 – 27.8%)* Delivery rate per transfer: **26.4%** *(Range: 14.2 – 38.7%)*	Clinical pregnancy rate per aspiration: **24.9%** *(Range: 13.8 – 37.3%)* Clinical pregnancy rate per transfer: **35.3%** *(Range: 14.8 – 58.3%)* Delivery rate per aspiration: **18.5%** *(Range: 8.7 – 31.3%)* Delivery rate per transfer: **26.2%** *(Range: 9.3 – 37.3%)*	Pregnancy rate per thawing: **34.6%** *(Range: 24.4 – 49.5%)* Pregnancy rate per transfer: ***35.5%*** *(Range: 23.4 – 50.4%)* Delivery rate per thawing: ***25.2%*** *(Range: 17.8 – 40.6%)* Delivery rate per transfer: ***25.7%*** *(Range: 17.1 – 41.4%)*
	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 oocyte aspiration and follicular flushing as part of 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 the media are consistent with the embryological competency limits and/or with the clinical ART outcomes described in the benchmark articles from the ESHRE.

There were several scientific articles retrieved from the literature studying the performance of Flushing Buffer's equivalent or similar devices. It can be concluded from these reports that embryological and clinical ART outcomes, when equivalent Flushing Buffer 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. 2022), suggesting a safe and adequate performance of Flushing Buffer when used for oocyte aspiration and follicular flushing as part of ART procedures, without damaging the patient's oocytes or ovarian follicles.

6.3 Device registers

In addition to the above, ART outcomes of two IVF clinics in Europe are included in the clinical evaluation report of Flushing Buffer (data not publicly available). Each clinic was asked to provide clinical data related with the use of equivalent media of Flushing Buffer in ART procedures performed during a certain period.

From the IVF clinics' data, it could be concluded that the obtained ART outcomes of all IVF centres are consistent with the embryology and ART outcomes published in the ESHRE reports (ESHRE Special Interest Group of Embryology 2017) and (Wyns et al. 2022), indicating that Flushing Buffer 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 evaluations of data pertaining to Flushing Buffer verification and validation testing, performance studies, device registries, client feedback and complaints, vigilance, and the state-of-the-art.

According to the multiple manuscripts available in the literature, the use of similar products to Flushing Buffer on the market demonstrates its performance and safety. Additionally, retrieved articles in which these devices have been used reported ART outcomes comparable with those published by the ESHRE.

Thus, from the literature data it could be concluded that devices with the same intended use as Flushing Buffer are able to aspirate oocytes and perform follicular flushing as part of ART procedures, without damaging the patient's oocytes or ovarian follicles.

Moreover, there is no evidence from the clinical data, literature articles, market/customer feedback and/or vigilance that the device is toxic for gametes or embryos, nor that the medium has a risk for cytotoxicity, material-mediated pyrogenicity, mutagenity, teratogenity, carcinogenity, oncogenicity, allergenicity or irritancy for patients and users.

Kitazato Corporation has taken all necessary steps to ensure that residual risks associated with the use of Flushing Buffer 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 Flushing Buffer 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 Flushing Buffer is not harmful to oocytes, ovarian follicles or patients, allowing oocyte aspiration and follicular flushing as part of ART procedures. No problems or complications were detected for Flushing Buffer.

The remaining risks identified in the Risk Assessment or other risks associated with oocyte aspiration and follicular flushing a using Flushing Buffer, 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.

There is sufficient evidence to establish the safety and performance of Flushing Buffer 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 Flushing Buffer. The device IFU clearly demonstrates safe use of Flushing Buffer and the mandatory medical training ensures all users are fully familiar with all aspects of device use.

Flushing Buffer 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 Flushing Buffer. Additionally, clinical data retrieved from IVF centers using Flushing Buffer will be evaluated.

This Summary of Safety and Clinical Performance will be refreshed with data from the post-market clinical follow-up, if this is 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 flushing buffers available on the market, reporting ART outcomes consistent with those published in the ESHRE benchmark report. Besides commercialized flushing buffers, there are no other alternative treatments for oocyte aspiration and follicular flushing as part of ART procedures.

8 Suggested profile and training for users

Flushing Buffer 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	12/09/2023	Initial version	Date: not yet Validation language: English
V.2	25/01/2024	Amended based on BSI (NB) MDR review	Date: not yet Validation language: English
V.3	28/05/2024	Amended product name and EU Rep address format	Date: 23/08/2024 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. Tandler-Schneider, I. A. Rugescu, and V. Goossens. 2022. 'ART in Europe, 2018: results generated from European registries by ESHRE', Hum Reprod Open, 2022: hoac022.