Summary of Safety and Clinical Performance

Gamete 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 it is intended to provide advice on the diagnostic or treatment of particular medical conditions to the intended users.

0 Abbreviations

IFU instructions for use
MDR Medical Device Regulation
NB notified body
PMCF post-market clinical follow-up
PMS post-market surveillance
PSUR periodic safety update report
SRN single registration number for an economic operator
SSCP summary of safety and clinical performance
TD technical documentation
UDI-DI Unique Device Identification - device identifier
ART Assisted Reproductive Technology
ESHRE European Society of Human Reproduction and Embryology
GMP Good Manufacturing Practice
HAS Human Albumin Solution
HSA Human Serum Albumin
HSSA Human Sperm Survival Assay
ICSI Intra Cytoplasmatic Sperm Injection

1 Device identification and general information

1.1 Device trade name(s)

-Gamete Buffer
-Gamete Buffer / SepaSperm Wash, with gentamicin and human albumin

1.2 Manufacturer's name and address

Kitazato Corporation
Address: 100-10 Yanagishima, Fuji, Shizuoka 416-0932 Japan
Phone: (+81) 545 65 7122 Fax: (+81) 545 65 7128
E-mail: ce_registration@kitazato.co.jp

1.3 Manufacturer's single registration number (SRN)

Kitazato Corporation SRN JP-MF-000018374

1.4 Basic UDI-DI

Gamete Buffer: 458223146GBDGL

1.5 Medical device nomenclature description/text

Applicable EMDN code: U08020503- Materials/culture media for assisted reproduction

1.6 Class of device

Gamete Buffer with or without human serum albumin (and SepaSperm wash) is considered medical devices Class III according to MDR (Regulation (EU) 2017/745) Annex VIII

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

Gamete Buffer without gentamicin and human albumin (class Iib

1.8 Authorized representative; name and the SRN

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C/Jorge Comín, 3, Bajo 1-2
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Tel +34 96 305 63 95
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SRN: SRN ES-AR-000014358

1.9 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

2 Intended use of the device

2.1 Intended purpose

Gamete Buffer is used for washing and handling of human gametes and embryos outside the incubator, during ICSI (Fertilization by intracytoplasmic sperm injection), IUI (Intra-uterine insemination) washing or swim-up of human spermatozoa and embryo transfer procedures.

2.2 Indication(s) and intended patient groups

Kitazato Gamete Buffer media are ready-to-use cell culture media designed to enable *in vitro* manipulation of gametes and embryos outside the CO_2 incubator, during ART-procedures (Assisted Reproductive Technologies procedures) of patients with infertility problems. Kitazato Gamete buffer can be used in combination with several assisted reproduction techniques such as IUI, IVF, ICSI and related.

Direct physical contact occurs between the media products and human gametes or embryos. With embryo transfer and IUI, the media come into direct contact with the uterus mucosal membranes of the patient.

Gamete Buffer media are used in specialized hospital laboratories by laboratory technicians, embryologists, medical doctors applying Assisted Reproductive Technologies (ART).

2.3 Contraindications and/or limitations

There are no known contraindications and/or limitations identified for Kitazato Gamete Buffer.

3 Device description

3.1 Description of the device

Gamete Buffer medium is a formulation for washing of human ova, spermatozoa and embryos. Gamete Buffer medium can also be used for swim-up techniques of human spermatozoa and for the preparation of density gradient media (with SepaSperm for example), for sperm injection in oocytes during Intracytoplasmic Sperm Injection (ICSI), for the introduction of washed spermatozoa in the uterus (IUI) and for embryo transfer. The medium is complete and needs no further additives. Gamete Buffer medium contains HEPES and is designed to enable in vitro manipulation of gametes and embryos outside the CO_2 incubator. It consists of a balanced salt solution supplemented with carbohydrate energy sources such as glucose, pyruvate and lactate. Relatively simple media, such as Gamete Buffer media, are not designed to support extended culture of cells and are therefore mainly used for cell isolation and handling.

The added gentamicin complies with Ph. Eur. Monograph Standard 0331, is EDQM-certified.

Gamete Buffer is not intended for single use, multiple single procedures can be performed with one bottle of Gamete Buffer.

The media can be used up to 7 days after bottle opening (when sterile conditions are maintained, and the products are stored at 2-8°C).

Gamete Buffer media are sterilized using aseptic processing techniques (filtration).

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

No previous generation of the devices have been brought on the market by Kitazato Corporation.

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

No accessories for Kitazato Gamete Buffer media are identified.

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

No devices and products for Gamete Buffer are identified.

4 Risks and warnings

4.1 Residual risks and undesirable effects

The inclusion of Human Serum Albumin, medical substance approved by the EMEA is the only residual risk in Gamete buffer solution concerning the transmission of viral or priori-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. As a consequence, standardization of the procedures remains difficult. Therefore, mouse embryo assay and human sperm survival tests are routinely performed as part of Gamete Buffer batch release criteria. **2.Transmission of viral or prion carried diseases due to the use of human derived protein source.** Along 50 years of clinical use, HSA is manufactured with a pasteurization procedure that has lead to an excellent viral safety. Only Plasbumin-25 or alternatively, Albunorm 25 will be used 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. In addition to the 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 guaranteed by any test method. The use of Gamete Buffer is restricted to gamete and embryos manipulation and is not intended to be in direct contact with users or patients. Even so, the instructions for use / MSDS clearly warn that the medium contains human albumin solution and that protective clothing should be worn.	1. Stabilization of the cell membrane of the embryo in the medium 2. Inhibition of lipid peroxidation that can be damaging to sperm 3. Carrier and source of essential molecules needed by the embryo 4. Detoxification by binding waste products from cell metabolism 5. Facilitating gamete/embryo manipulation by preventing adsorption to the surface through saturation of potential binding sites

Based on this analysis above it is concluded that the benefit of adding HSA to the media outweighs the risk and the overall residual risk related to the use of Gamete Buffer medium with inclusion of HSA has been judged acceptable.

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

- 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.

- 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.

No other known undesirable side-effects are identified.

4.2 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 • Do not use if packing is damaged or broken. • Do not use if product becomes cloudy or shows evidence of microbial contamination.	• Always works under strict hygienic conditions (e.g. LAF bench ISO class 5) to avoid contamination. Aseptic technique should be used. • In case of eye or skin contact with Gamete Buffer, immediately flush eye/skin with water. • Observe all federal, state and local environmental regulations when discarding the product. • In case of infection, dispose the product appropriately in a prescribed manner. • The user shall be responsible for any problems caused by non-conformity to the present IFU. • This product is intended to be used by medical specialist trained in fertility treatment.

4.3 Summary of any field safety corrective action (FSCA including FSN)

No field safety corrective actions with regard to Gamete Buffer were needed.

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

5.1 Summary of clinical data related to similar/equivalent devices

Gamete Buffer is equivalent/similar to following marketed devices:
Media with similar intended use generally consist of balanced salt solutions and energy substrates. Most of the media are supplemented with HSA (concentrations range from 3.5-10 g/liter), and can/or are provided supplemented with gentamicin (usually at a concentration of 10 g/liter)

- Sydney IVF Gamete Buffer / Sydney IVF sperm medium (Cook Medical)
- GM501 Wash, GM501 SpermAir, GM501 SpermActive (Gynemed)
- Multipurpose Handling Medium with Gentamicin (Irvine Scientific)
- Sperm Wash, Sperm Preparation Medium (Origio)
- G-Gamete (Vitrolife)
- V-HEPES plus, V-Sperm Wash (Vitromed)
- FertiCult Flushing Media (FertiPro) Basic UDI-DI 5411967FLUSH1WY. Following clinical data was obtained:

5.2 Summary of clinical data from literature

According to multiple manuscripts available in the literature, the use of products on the market similar to Gamete Buffer demonstrates their performance and safety (Stigliani et al., 2021) (Petersen et al., 2019) (Rehnitz et al., 2020) (Kim et al., 2015) (Ciepiela et al., 2007) (Marchetti et al., 2002).
Additionally, papers where these devices have been implemented have reported ART outcomes comparable with the ART outcomes published by the European Society of Human Reproduction and Embryology (ESHRE).
Thus, from the literature data it could be concluded that devices with the same intended use than Gamete Buffer, are not detrimental for fertilization and embryo development, without interfering with the general ART procedure.

5.3 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%)

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 1197 institutions in 29 countries, with a total of 918.159 treatment cycles (covering the time period from 1 January to 31 December 2016) C. Wyns et al., ART in Europe, 2016: results generated from European registries by ESHRE. Hum Reprod Open. 2020; 2020(3) (Wyns et al. 2020) and is summarized in the table below:

ART in Europe, 2016: results generated from European registries by ESHRE	**In vitro fertilization (IVF):**	**Intra cytoplasmic sperm injection (ICSI):**	**Frozen embryo replacement (FER):**	**Intrauterine insemination(IUI):** **using husband semen (IUI-H):**
A total of 918 159 treatment cycles, involving 156 002 with IVF, 407 222 with ICSI, 248 407 with frozen	Clinical pregnancy rate per aspiration: **28.0%**	Clinical pregnancy rate per aspiration: **25%**	Pregnancy rate per thawing: **30.9%**	

embryo replacement (FER), 27 069 with preimplantation genetic testing (PGT), 73 927 with egg donation (ED), 654 with IVM of oocytes and 4878 with FOR (frozen oocyte replacement) were recorded. European data on IUI using husband / partner's semen (IUI-H) and donor semen (IUI-D) were reported from 1197 institutions offering IUI in 29 countries and 24 countries, respectively. A total of 162 948 treatments with IUI-H and 50 467 treatments with IUI-D were included.	*(range: 13.2 - 57.1%)* Clinical pregnancy rate per transfer: **34.8%** *(range: 22.4 - 69.5%)* Delivery rate per aspiration: **20.8%** *(range: 9.8 - 33.9%)*	*(range: 18.7 - 41.9%)* Clinical pregnancy rate per transfer: **33.2%** *(range: 25.6 - 70.3%)* Delivery rate per aspiration: **18.5%** *(range: 12.3 - 46.5%)*	*(range: 21.4 - 51.9%)* Pregnancy rate per transfer:**31.9%** *(range: 22.5 – 57.6%)* Delivery rate per thawing: **22.0%** *(range: 13.0 - 45.3%)* Delivery rate per transfer: **22.7%** *(range: 13.0 - 47.6%)*	Delivery rate per cycle: **8.9%** *(range: 0.9 - 24.7%)* **using donor semen (IUI-D):** Delivery rate per cycle: **12.4%** *(range: 5.1 - 44.4%)*
	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 gamete/embryo washing/handling and 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 paper can therefore be considered as benchmark data for ART procedures. Nevertheless, when comparing clinical data, one should be aware that:

- ✓ During ART processes, gametes/embryos come into 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.

A literature search is performed to investigate whether embryological and/or clinical ART outcomes obtained during literature search are consistent with the embryological competency limits and/or with the clinical ART outcomes described in the benchmark papers from the ESHRE.
There were several papers retrieved in literature studying the performance of Gamete Buffer media equivalent or similar devices. It can be concluded from these papers that embryological and clinical ART outcomes, when equivalent Gamete Buffer media are used, fall within the range of the outcomes described in the benchmark papers from the ESHRE (Wyns et al. 2020) (ESHRE Special Interest Group of Embryology 2017), suggesting a safe and adequate performance of media.

Papers describing the use of Gamete Buffer equivalent and/or similar media ***for washing ova, spermatozoa and embryos***

(Benchaib et al. 2007)
(Frydman et al. 2008)
(Huang et al. 2005)
(Fauque et al. 2010)
(Benchaib et al. 2005)
(Le Du et al. 2005)
(Barraud-Lange et al. 2011)
(Pont et al. 2012)
(Falah et al. 2014)
(Desch et al. 2015)
(Jansen et al. 2017)
(Le Bras et al. 2017)
(Llabador et al. 2015)
(Philippon et al. 2015)
(Fournier et al. 2018)
(Hachemi et al. 2019)
(Delaroche et al. 2021)
(Mayeur et al. 2020)
(Puy et al. 2020)

Papers describing the use of Gamete Buffer equivalent and/or similar media ***for sperm injection in oocytes during ICSI***

(Ledee et al. 2008)
(Ledee et al. 2010)
(Abbas et al. 2020)

Papers describing the use of Gamete Buffer equivalent and/or similar media ***for the introduction of washed spermatozoa in the uterus (IUI)***

(Barraud-Lange et al. 2011)
(Pont et al. 2012)
(Jansen et al. 2017)
(Vichinsartvichai, Traipak, and Manolertthewan 2018)
(Vichinsartvichai et al. 2015)
(Ruiter-Ligeti et al. 2020)

Papers describing the use of Gamete Buffer equivalent and/or similar media ***for the preparation of density gradient***

(El Khattabi et al. 2013)

Papers describing the use of Gamete Buffer equivalent and/or similar media ***for washing ova, spermatozoa and embryos AND for the preparation of density gradient***

(Dupont et al. 2015)
(Sifer et al. 2014)
(Herbemont et al. 2017)
(Vichinsartvichai, Traipak, and Manolertthewan 2018)
(Vichinsartvichai et al. 2015)
(Buffat et al. 2006)
(Parmegiani et al. 2012)
(Beauvillard et al. 2015)

Clinical data from equivalent media obtained from real-world evidence are consistent with the outcomes described in this benchmark paper to assess clinical safety and performance as well as benefit-risks of the media.

5.4 Device registers

In addition, clinical data is obtained from IVF centers in Europe that use Gamete Buffer equivalent medium. ART outcomes of these clinics are consistent with clinical outcomes described in national public registers of the countries in which the IVF centers are located or with the ART outcomes as described in the benchmark paper from the ESHRE (Wyns et al. 2020). The outcomes can be considered as benchmark data, as these national outcomes are generated with equivalent or a similar device available on the market.

IUI outcomes from the years 2017 and 2018 of two IVF clinics located in Europe (details are confidential) are included in the clinical evaluation report of Gamete Buffer medium. It could be concluded that the IUI results of these IVF clinics (282 cycles) are consistent with clinical outcomes described in the national public registers of the country. Also, ART outcomes from an IVF center in the Netherlands (2611 IVF cycles, 2025 ICSI cycles and 4722 cryo transfers) generated between 2013 to 2019 are consistent with the national outcomes. Next, ART outcomes of 2666 IVF/ICSI procedures performed in 2018 and 5671 IVF/ICSI procedures performed in 2019 (>80% of the procedures are ICSI) generated in 5 clinics in an European country (details are confidential) are consistent with the outcomes reported in the benchmark ESHRE article. This all indicates a good and safe performance of Gamete Buffer medium.

5.5 An overall summary of the clinical performance and safety

Gamete Buffer should be able to maintain a stable, non-toxic and pathogen-free environment. As gametes and embryos are highly sensitive to minimum changes in their milieu, the outcome of ART procedures will be inevitably affected by small fluctuations of temperature and alterations of physical properties of media (pH and osmolality). Thus, Gamete Buffer has to provide an optimal condition without being detrimental for fertilization and embryo development.
According to the information from the clinical evaluation report, it can be concluded that Gamete Buffer functions as stated by the manufacturer. Gamete Buffer media, support handling of gametes and embryos during in vitro manipulation outside the CO_2 incubator without leading to a detrimental effect on ART outcomes. Furthermore, also the literature search of similar devices on the market with the

same intended use, demonstrate the performance and safety of Gamete Buffer are consistent with competency limits reported by ESHRE (Wyns et al. 2020)

Moreover, no infrequent complications or problems were detected.

5.6 Ongoing or planned post-market clinical follow-up

On a yearly basis, Kitazato Corporation will perform literature search for Gamete Buffer as well as for Human Serum Albumin component and for gentamicin. Additionally, clinical data retrieved from IVF centers using Gamete Buffer media 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.

6 Possible diagnostic or therapeutic alternatives

Multiple articles available in the literature demonstrate comparable results among the different media on the market with the same intended use of Gamete Buffer, reporting ART outcomes comparable with the ART outcomes published by the European Society of Human Reproduction and Embryology (ESHRE).

7 Suggested profile and training for users

Gamete Buffer are used in specialized laboratories performing fertilization techniques, including IVF, ICSI and sperm preparation/analysis. The intended users are IVF professionals (lab technicians, embryologists, or medical doctors).

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

The following guidance document was used:
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)

9 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
1	2021/03/02	Initial version	Date: not yet validated Validation language: English
2	2022/05/12	Updated from BSI assessment review	Date: not yet validated Validation language: English
3	2022/05/18	Updated from BSI assessment review	Date: not yet validated Validation language: English

4	2023/11/29	Updated from BSI assessment review	Date: 30/11/2023 Validation language: English

10 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.

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