Summary of Safety and Clinical Performance

SepaSperm

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

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

2 Device identification and general information

2.1 Device trade name(s)

SepaSperm:

- SepaSperm Solution
- SepaSperm Solution with Gentamicin
- SepaSperm 45%
- SepaSperm 90%

2.2 Manufacturer’s name and address

Kitazato Corporation
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2.3 Manufacturer’s single registration number (SRN)

JP-MF-000018374

2.4 Basic UDI-DI

458223146SEPKH

2.5 Medical device nomenclature description/text

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

2.6 Class of device

SepaSperm Solution, SepaSperm Solution with Gentamicin, SepaSperm 45%, SepaSperm 90% is 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

SepaSperm Solution 2022

2.8 Authorized representative if applicable; name and the SRN

Biomedical Supply, S.L.(Dibimed)
3 Jorge Comín
46015 Valencia, Spain

SRN: ES-AR-000014358

2.9 NB's name and single identification number

BSI Group The Netherlands B.V.
NB identification number: 2797

3 Intended use of the device

3.1 Intended purpose

SepaSperm Solution (with and without gentamicin) is a ready to use medium used for separation of motile sperm from seminal fluid with density gradient method.

SepaSperm Solution (with and without gentamicin) is a stock solution used for the preparation of density gradients, while SepaSperm 45% and SepaSperm 90% are ready to use density gradients.

They are discontinuous gradient systems which effectively separate spermatozoa from seminal plasma. During centrifugation, cells move through the discontinuous density gradient to the point in the gradient which matches their own density.

3.2 Indication(s) and intended patient groups

SepaSperm media can be used as a sperm preparation method for further use in Intra Uterine Insemination (IUI), In Vitro Fertilization (IVF) Intra-Cytoplasmic Sperm Injection (ICSI), and related Assisted Reproductive Technologies (ART).

SepaSperm media centrifugation is such a rapid and powerful method for separating motile spermatozoa from other cell types present in human donor and partner semen (including immotile spermatozoa, debris, contaminating leukocytes and seminal plasma), without causing damage to the gametes before assisted reproduction treatments (either IUI, IVF or ICSI).

SepaSperm media is used during ART procedures of patients with infertility problems.

SepaSperm media is 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).

3.3 Contraindications and/or limitations

There are no known contraindications and/or limitations identified for SepaSperm Solution, SepaSperm Solution with Gentamicin, SepaSperm 45% and SepaSperm 90%.

4 Device description

4.1 Description of the device

The products described in this summary are SepaSperm (either in stock solution or in prepared gradient), which effectively separate spermatozoa from seminal plasma.

During centrifugation, cells move through the discontinuous density gradient to the point in the gradient which matches their own density. Once in centrifugation, the cells move through the gradient until the gradient that matches their own density. As result, a pellet containing the most good-quality spermatozoa is produced.

SepaSperm is an isotonic solution of silane-coated silica particles in Earle's Balanced Salt Solution (EBSS) with HEPES (pH buffer).

SepaSperm Solution is also available with Gentamicin (10 mg/l, medicinal substance) as SepaSperm Solution with Gentamicin. SepaSperm 45% and SepaSperm 90% contain gentamicin. The added gentamicin complies with Ph. Eur. Monograph Standard 0331, is EDQM-certified and is approved by the MHRA (Medicines and Healthcare Products Regulatory Agency).

SepaSperm 45% and SepaSperm 90% contains Human Serum Albumin. The EMA (European Medicine Agency) has approved the inclusion of Human Serum Albumin in Kitazato ART media.

SepaSperm media are not intended for a single use but multiple single procedures can be performed with one bottle of product. The media can be used in combination with several assisted reproduction procedures such as IUI, IVF, ICSI and related ART. 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).

SepaSperm Solution, SepaSperm Solution with Gentamicin, SepaSperm 45% and SepaSperm 90% are sterilized (SAL 10-3) using aseptic processing techniques (filtration).

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 European Union market by Kitazato Corporation.

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

No accessories for SepaSperm Solution, SepaSperm Solution with Gentamicin, SepaSperm 45% and SepaSperm 90% are identified.

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

SepaSperm Solution / SepaSperm Solution with Gentamicin might be used with Gamete Buffer/SepaSperm Wash manufactured by Kitazato.

5 Risks and warnings

5.1 Residual risks and undesirable effects

The inclusion of Human Serum Albumin (HSA) in SepaSperm 45% and SepaSperm 90% is approved by the EMEA. This is the only residual risk, concerning the eventual 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. 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) and human sperm survival assays are routinely performed as part of SepaSperm 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 led 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 his moment, full assurance that products derived from human blood will not transmit infectious agents cannot be granted by any test method. The use of SepaSperm is restricted to the sperm preparation 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. Inhibition of lipid peroxidation that can be damaging to sperm. 2. Detoxification by binding waste products from cell metabolism. 3. HSA prevents cell aggregation and adherence to laboratory equipment and promotes the ease of gamete handling and manipulation

Based on the 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 SepaSperm 45%, SepaSperm 90% with inclusion for human serum albumin for semen preparation has been judged acceptable.

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

- 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.

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. • Do not use if packing is damaged or broken. • Do not use if product becomes cloudy or shows evidence of microbial contamination. • Product should not be used on a patient that has known allergy to gentamicin or similar antibiotics.	SepaSperm Solution / SepaSperm Solution with Gentamicin: • Aseptic technique should be used. • Use sterilized equipment and materials only. • In case of eye or skin contact with SepaSperm Solution, 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 non-conformity to the present IFU. • This product is intended to be used by medical specialist trained in fertility treatment. SepaSperm 45% and 90%: • For addition of human albumin to the medium, it is strongly recommended to follow the procedure prescribed in the section ‘Preparation of working solution’. • Aseptic technique should be used • Use sterilized equipment and materials only. • In case of eye or skin contact with SepaSperm, 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 or not following the present IFU.

	• This product is intended to be used by medical specialist 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.

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

No field safety corrective actions with regard to SepaSperm Solution, SepaSperm Solution with Gentamicin, SepaSperm 45% and SepaSperm 90% 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 SepaSperm approvals and registrations. There is sufficient data available from its clinical use to demonstrate safety and performance.

SepaSperm family is equivalent/similar to the following devices:

Company	Product name
Cook Medical	Sydney IVF Spermient and Sydney IVF Sperm Gradient
Fertipro	Density Gradient Media: Sil-select Stock, Sil-select stock with Gentamicin; Sil-select plus upper layer with Gentamicin; Sil-select plus lower layer with Gentamicin
Genea Biomedx (Merck)	Sperm Wash Gradient media
Gynemed	GM501 Gradient media
Gynotec	SpermTec G media
	SpermFilter® media
Irvine Scientific	Isolate media
Kitazato	SepaSperm solution media (without HSA)
LifeGlobal	AILGrad media

Nidacon	PureSperm media
Origio	Gradient media
	SupraSperm media
Sage	PureCeption Sperm Separation media
Vitrolife	SpermGrad media
Vitromed	V-GRAD media

Basic UDI-DI of Density Gradient Media: 5411967DENSG1S5

The evaluation included the analysis of the clinical data from the equivalent device from scientific literature review.

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%)

Clinical ART data obtained from IVF centres should be consistent with the clinical outcomes described in the benchmark paper from the ESHRE (Wyns et al. 2021).

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):**
A total of 918 159 treatment cycles, involving 156 002 with IVF, 407 222 with ICSI, 248 407 with frozen 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	Clinical pregnancy rate per aspiration: **28.0%** *(range: 13.2 - 57.1%)* Clinical pregnancy rate per transfer: **34.8%** *(range: 22.4 - 69.5%)*	Clinical pregnancy rate per aspiration: **25%** *(range: 18.7 - 41.9%)* Clinical pregnancy rate per transfer: **33.2%** *(range: 25.6 - 70.3%)*	Pregnancy rate per thawing: **30.9%** *(range: 21.4 - 51.9%)* Pregnancy rate per transfer:**31.9%** *(range: 22.5 – 57.6%)* Delivery rate per thawing: **22.0%**	**using husband semen (IUI-H):** Delivery rate per cycle: **8.9%** *(range: 0.9 - 24.7%)* **using donor semen (IUI-D):** Delivery rate per cycle: **12.4%**

countries and 24 countries, respectively. A total of 162 948 treatments with IUI-H and 50 467 treatments with IUI-D were included.	Delivery rate per aspiration: **20.8%** *(range: 9.8 - 33.9%)*	Delivery rate per aspiration: **18.5%** *(range: 12.3 - 46.5%)*	*(range: 13.0 - 45.3%)* Delivery rate per transfer: **22.7%** *(range: 13.0 - 47.6%)*	*(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 separation of motile sperm from seminal fluid 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 paper can therefore be considered as benchmark data for ART procedures. Nevertheless, when comparing clinical data, one should be aware that:

- ✓ During ART processes, sperm 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.

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.

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 SepaSperm family equivalent or similar devices. It can be concluded from these papers that embryological and clinical ART outcomes, when equivalent SepaSperm family 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 SepaSperm family and then it is as such able to select for highly motile cells with elevated DNA integrity, without being detrimental for fertilization and embryo development.

Selected articles describing the performance and/or safety of SepaSperm family:

(Trokoudes et al. 2005)
(Vichinsartvichai et al. 2015)
(Le et al. 2021)
(Dal Canto)
(Tam Le et al. 2019)
(Kaewman et al. 2021)
(Antinori et al. 2008)
(Naji et al. 2018)
(Giebler et al. 2021)
(Berkovitz et al. 2005)
(La Marca et al. 2019)
(Rex et al. 2021)
(Berkovitz et al. 2006)
(Soysal and Ozmen 2018)
(Fadini et al. 2011)
(Renzini et al. 2017)
(Honda et al. 2015)
(Fujii et al. 2020)
(Fadini et al. 2015)
(Dal Canto et al. 2021)

6.3 Device registers

In addition to the above, ART outcomes of nine IVF clinics located in Europe are included in the clinical evaluation report of SepaSperm family (data not publicly available). IVF centers were asked to provide clinical data using SepaSperm family or when ART data is published in national registers, to sign a statement that SepaSperm family were used during their ART procedures during a certain time period.

Overall, it could be concluded that the ART outcomes of the IVF centres are consistent or above the national averages of their country or are consistent with the ART outcomes published in the ESHRE paper (Wyns et al. 2021), indicating that SepaSperm family of FertiPro NV does not interfere with the general ART procedures.

6.4 Summary of clinical data from other sources

The clinical evaluation also included evaluations of data pertaining to SepaSperm from verification and validation testing, performance studies, device registries, client feedback and complains, vigilance and the state-of-the-art.

According to the multiple manuscripts available in the literature, the use of products on the market similar to SepaSperm demonstrates their performance and safety. 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 SepaSperm are able to select for highly motile cells with elevated DNA integrity, 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 SepaSperm 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 SepaSperm, 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 study, it can be concluded that SepaSperm Solution, SepaSperm Solution with Gentamicin, SepaSperm 45% and SepaSperm 90% are not harmful for fertilization and embryo development, allowing the selection of motile spermatozoa with elevated DNA integrity. No problems or complications were detected for SepaSperm Solution, SepaSperm Solution with Gentamicin, SepaSperm 45% and SepaSperm 90%.

The remaining risks that have been identified in the Risk Assessment or other risks associated with the separation of motile sperm from seminal fluid with density gradient method, 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 the SepaSperm 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 confirm the safety and performance of the SepaSperm. The SepaSperm IFU clearly demonstrates safe usage of the device and mandatory physician training ensures all users are fully conversant with all aspects of device use.

SepaSperm 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 SepaSperm Solution, SepaSperm Solution with Gentamicin, SepaSperm 45% and SepaSperm 90%. Additionally, clinical data retrieved from IVF centers using SepaSperm Solution, SepaSperm Solution with Gentamicin, SepaSperm 45% and SepaSperm 90% 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 articles available in the literature demonstrate comparable results among the different density gradient media on the market, reporting ART outcomes comparable with the ART outcomes published by the European Society of Human Reproduction and Embryology (ESHRE).

8 Suggested profile and training for users

SepaSperm Solution, SepaSperm Solution with Gentamicin, SepaSperm 45% and SepaSperm 90% 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).

9 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)

10 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
V.0	20/07/2022	Initial version	Date: not yet Validation language: English
V.1	09/05/2023	First version	Date: 05/10/2023 Validation language: English This version has been approved by the Notified Body.

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

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