Summary of Safety and Clinical Performance

PVP

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 for Use (IFU), which is the main document to ensure the safety of the device, and neither is it intended to provide advice on the diagnostic or therapeutic suggestions to the intended users.

0 Abbreviations

ART Assisted Reproductive Technology
EMA European Medicine Agency
EMDN European Medical Devices Nomenclature
ESHRE European Society of Human Reproduction and Embryology
FSCA Field Safety Corrective Action
FSN Field Safety Notice
HAS Human Albumin Solution
HbsAg Hepatitis B surface Antigen
HBV Hepatitis B Virus
HCV Hepatitis C Virus
HEPES 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HIV Human Immunodeficiency Virus
HSA Human Serum Albumin
HSSA Human Sperm Survival Assay
ICSI Intra Cytoplasmatic Sperm Injection
IFU instructions for use
IVF In Vitro Fertilization
MDR Medical Device Regulation
MEA Mouse Embryo Assay
MSDS Material Safety Data Sheet
NB notified body
PMCF post-market clinical follow-up
PVP polyvinyl pyrrolidone
SRN single registration number for an economic operator
SSCP summary of safety and clinical performance
UDI-DI Unique Device Identification - Device Identifier

1 Device identification and general information

1.1 Device trade name(s)

Product trade Name: PVP

Variants:

Product code	Product reference
PVPD10-0.2x5	95910
PVPD10-1	95901

1.2 Manufacturer's name and address

Kitazato Corporation
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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

458223146PVPLM

1.5 Medical device nomenclature description/text

Applicable EMDN code: U08020502 - Materials/solutions for preparation/handling for assisted reproduction.

1.6 Class of device

PVP media are 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

PVP (class III under Medical Device Regulation (MDR) (EU) 2017/745 Annex IX Chapter II): MDR 760763 and MDR 760355, First issued 27/06/2024.

1.8 Authorised representative; name and the SRN

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SRN: ES-AR-000014358

1.9 Notified Body's name and single identification number

British Standards Institution Group (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

PVP Medium is intended to be used to decrease the sperm motility during Intra-Cytoplasmatic Sperm Injection (ICSI).

2.2 Indication(s) and intended patient groups

ICSI procedures require the capture of individual sperm cells in a glass pipette for injection into the oocyte. This is facilitated by first placing the sperm in a viscous medium like PVP to decrease spermatozoon motility and subsequently nick their tails to immobilize them completely. Therefore, PVP is indicated for decreasing sperm motility during ICSI procedures.

The intended target population are patients undergoing Assisted Reproductive Technology (ART) procedures, which are typically indicated as treatments for patients with infertility problems.

2.3 Contraindications and/or limitations

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

2.4 Approved version of the IFUs

2.2 IFU_PVP_2024_V4, version 4, 2024-02

3 Device description

3.1 Description of the device

The product described in this summary is PVP, which is typically used to decrease the sperm motility during ICSI. PVP is a ready-to-used viscous medium composed of physiologic salts, HEPES, glucose, pyruvate, lactate, 10% (w/v) polyvinylpyrrolidone (Ph Eur grade) and Human Serum Albumin (4.0 g/l). The inclusion of Human Serum Albumin (HSA) in PVP is approved by the EMA.

Direct physical contact occurs between the media and human sperm cells. There is no direct or indirect contact with the human body.

PVP is not intended for single use; multiple single procedures can be performed with one bottle. The medium can be used up to 7 days after bottle opening (when sterile conditions are maintained, and the products are stored at 2-8°C).

PVP is 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 generations of the device 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 PVP are identified.

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

No specific devices and products to be used in combination with PVP are identified. The product can be used in combination with general ART media and labware.

4 Risks and warnings

4.1 Residual risks and undesirable effects

The inclusion of Human Serum Albumin (HSA), a medical substance approved by the EMA, is the only residual risk in PVP and concerns the transmission of viral or prion-carried diseases and the batch-to-batch variation associated with the inclusion of HSA in the media. 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 (MEA) is routinely performed as part of the batch release criteria of HSA (incoming inspection) and human sperm survival assays (HSSA) and MEA tests are routinely performed as part of PVP 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 excellent viral safety. Only Human Serum Albumin products approved by the European Medicines Agency (EMA) and covered by a valid Plasma Master File are used as the source of albumin, as the EMA has positively evaluated the usefulness, safety and benefit of their inclusion 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 granted by any test method. The use of PVP is restricted to 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 by preventing adsorption to the surface through saturation of potential binding sites. 4. pH regulator. 5. Osmotic regulator: Stabilization of the cell membrane of the embryo in the medium. 6. Carrier and source of essential molecules needed by the embryo.

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 PVP with inclusion for HSA has been judged acceptable.

Accordingly, the Instructions for Use (IFU) 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.

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.	• Aseptic technique should be used. • Use sterilized equipment and materials only. • In case of eye or skin contact with PVP 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 pre-pared 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. • Avoid multiple openings of the container. Take the required volume from the container to an appropriate sterile recipient and once finished, discard unused media from the recipient to avoid contamination. • Presence of human albumin in the PVP solution may occasionally cause a small amount of precipitation in the medium on the slide or dish.

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

No field safety corrective actions with regard to PVP 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

Kitazato Corporation has performed a clinical evaluation to support PVP approvals and registrations. There is sufficient data available from its clinical use to demonstrate its safety and performance. Kitazato PVP is equivalent/similar to the following marketed devices:

- GM501 PVP (Gynemed)
- 7% PVP Solution with HAS / 10% PVP Solution with HAS / PVP-Lyophilized (Irvine Scientific)
- PVP (LifeGlobal)
- SpermCatch (Nidacon)
- SpermSlow / PVP Clinical Grade / PVP Medium (Origio)
- PVP 7% (w/v) in HEPES-HTF (Sage)
- ICSI (Vitrolife)
- V-PVP 7 (Vitromed)
- Sydney IVF PVP (Cook Medical)
- 10% PVP in FertiCult Flushing medium (FertiPro). Basic UDI-DI: 5411967PVP169.

The evaluation included the analysis of the clinical data from equivalent/similar devices from scientific literature review.

5.2 Summary of clinical data from literature

It is expected that the clinical outcomes from ART procedures performed at IVF centres in which PVP media are used, are consistent with two main publications, used as reference for the standard competency values for ART outcomes (i) the embryology ART outcomes (i.e. ICSI fertilization rate, blastocyst development rate) published in the article from the ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine on the development of ART laboratory performance indicators, and (ii) the clinical ART outcomes reported in the annual peer-reviewed benchmark article of the European Society of Human Reproduction and Embryology (ESHRE).

According to the Vienna consensus – resulting from an expert meeting by the ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine in 2017 on ART laboratory performance inficators – the competency limits for fertilization rate and blastocyst development rate were:

- ICSI normal fertilization rate: **≥65%** (lower range: 55%)
- Blastocyst development rate: **≥40%** (lower range: 30%)

Since multiple factors can have an influence on the embryology outcomes, a value 10% lower than the competency limit defined by ESHRE is considered acceptable.

Moreover, the ESHRE yearly collects, analyses and reports ART data generated in Europe. The most recent report (Smeenk *et al.,* 2023) includes data from 1,487 institutions in 40 countries, with a total of 1,007,813 treatment cycles, 427,980 of which were performed using ICSI (covering the time period from 1 January to 31 December 2019). For cycles performed using ICSI, the competency standards were reported as:

- Clinical pregnancy rate per aspiration: **24.9%** (range: 16.0-46.1%)
- Clinical pregnancy rate per transfer: **37.2%** (range: 26.9-52.1%)
- Delivery rate per aspiration: **17.8%** (range: 10.6-28.6%)
- Delivery rate per transfer: **27.0%** (range: 12.1-39.4%)

Since multiple factors can have an influence on the ART outcomes (ART treatment, patients characteristics, laboratory procedures, etc.), a value within the range of the ESHRE values is acceptable.

As there are no alternative treatment options that can be used for reducing the motility of sperm during ICSI 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.

A literature search is performed annually to investigate whether embryology and/or clinical ART outcomes obtained from the use of the devices or their equivalent are consistent with the embryology and/or the clinical ART outcomes described in the benchmark papers from the ESHRE.

There were several papers retrieved in literature studying the performance of PVP equivalent devices. It can be concluded from these papers that embryological and clinical ART outcomes fall within the range of the outcomes described in the benchmark papers from the ESHRE (Smeenk et al. 2023) (ESHRE Special Interest Group of Embryology 2017), suggesting a safe and adequate performance of PVP to decrease sperm motility during ICSI procedures. Selected articles describing the performance and/or safety of PVP family are listed in Section 11. References.

Moreover, none of the retrieved scientific articles using these devices reported toxicity of the media for gametes and/or resulting embryos or any risk for cytotoxicity, allergenicity, irritancy, mutagenicity, carcinogenicity, oncogenicity or teratogenicity for patients and users, demonstrating the safety of the device. Thus, from the literature data it could be concluded that PVP media are not detrimental for human sperm used for ICSI, and do not interfere with the general ART procedure.

5.3 Summary of real-world clinical data from IVF clinics

In addition to the above, real-world ART outcomes from multiple IVF clinics in Europe and other regions were evaluated as part of the Clinical Evaluation Report. The results were consistent with, or above, national averages and the ART outcomes published in the ESHRE benchmark report (Smeenk et al., 2023).

All these clinical data evidence the safety and excellent performance of PVP media and demonstrates the device does not interfere with ART procedures when used according to the instructions for use.

5.4 Vigilance analysis and customer/market feedback

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

No emerging risks, systematic missuse, previously unknown side effects or contra-indications were identified from vigilance activities and client feedback/complaint analysis of PVP devices. Additionally, there there were no incidents and/or field safety corrective actions taken related to the clinical and safe use of the device.

The vigilance and complaints information included in this SSCP is derived from Kitazato's Post-Market Surveillance (PMS) system, including the Periodic Safety Update Report (PSUR) KTZ-PSUR-PVP-2024-0001. It covers the period from 26 June 2024 (date of CE certification) to 27 December 2024, and is based on the data consolidated in the Technical Documentation, PMS and Clinical Evaluation Report.

5.5 An overall summary of clinical performance and safety

According to the information exposed in the clinical evaluation report, it can be concluded that PVP functions as stated by the manufacturer and that no complications, incidents or adverse events have been reported. There is no evidence that the device poses any risk of toxicity for gametes or resulting embryos, or of cytotoxicity, allergenicity, irritancy, mutagenity, carcinogenity, oncogenicity or teratogenity for patients and users.

Literature searches for PVP as well as the equivalent and similar devices on the market with a shared intended use further demonstrate that the device is safe and performs as intended, since the obtained clinical outcomes are consistent with competency limits reported by ESHRE (ESHRE Special Interest Group of Embryology, 2017; Smeenk et al., 2023); and no complications were detected during the assessment of the literature.

Kitazato Corporation has taken all necessary steps to ensure that residual risks associated with the use of PVP 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. The only residual risk identified is associated with the fact that this medium contains a human blood derivative (HSA). Based on the risk-benefit analysis conducted it is concluded that the benefit of adding HSA to the medium outweighs the risk; therefore, this residual risk is acceptable.

There is sufficient evidence to establish the safety and performance of PVP 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, this 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 PVP. The PVP Instructions for Use (IFU) clearly demonstrates safe usage of the device and mandatory physician training ensures all users are fully conversant with all aspects of device use. PVP has been confirmed to be within the current state-of-the-art practice.

5.6 Ongoing or planned post-market clinical follow-up

On a year basis, Kitazato Corporation will perform Post-Market Clinical Follow-up for PVP, including literature searches, screening of device registers for clinical data, complaint/customer feedback and vigilance analysis, and clinical data retrieved from In Vitro Fertilization (IVF) centers using PVP.

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

6 Possible diagnostic or therapeutic alternatives

ICSI procedures require the capture of individual sperm cells in a glass pipette for injection into the oocyte and this is facilitated by first immobilizing the sperm by placing them in a viscous medium like PVP medium

prior to nicking the tail to immobilize sperm completely. Multiple articles available in the literature demonstrate comparable results among the different PVP medium on the market, reporting ART outcomes comparable with the ART outcomes published by the ESHRE. Although alternative procedures for spermatozoa selection in ICSI, such as Hyaluronic Acid, have been described (reviewed by (Simopoulou et al. 2016)), PVP remains the most used medium in ART laboratories for the specific purpose of reducing sperm motility for a more adequate evaluation by the embryologist and to allow for their manipulation with the injection pipette (to select the appropriate sperm among the many present in the sample drop and to immobilize them prior to their injection into the oocyte (Simopoulou et al. 2016).

7 Suggested profile and training for users

PVP is used in specialized laboratories performing fertilization techniques including IVF, ICSI and sperm preparation/analysis. The intended users are medical specialists trained in fertility treatment (laboratory technicians, andrologists, embryologists, or medical doctors).

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

The following guidance documents were used:

- MDCG 2019-09: Summary of safety and clinical performance. A guide for manufacturers and notified bodies Rev.1 (March 2022).
- ISO 13408-1:2023 / EN ISO 13408-1:2024: Aseptic processing of health care products – Part 1: general requirements (fully applicable).
- (EN) ISO 13408-2:2018: Aseptic processing of health care products – Part 2: Filtration (fully applicable).
- ISO 13485:2016 / EN ISO13485:2016/Amd 11:2021: Medical devices — Quality management systems — Requirements for regulatory purposes (fully applicable).
- EN 556-2:2024: Sterilization of medical devices – Requirements for medical devices to be designated 'STERILE' –Requirements for aseptically processed medical devices (fully applicable).
- (EN) ISO 20417:2021: Information to be supplied by the manufacturer (fully applicable).
- ISO 10993-1:2018 / EN ISO 10993-1:2020 + A11:2021 Biological evaluation of medical devices -- Part 1: Evaluation and testing (fully applicable).
- EN ISO 10993-5:2009/A11:2025 Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity (fully applicable).
- ISO 10993-18:2020/Amd 1/2022 / EN ISO 10993-18:2020/A1:2023: Biological evaluation of medical devices – Part 18: Chemical characterization of medical device materials within a risk management process (fully applicable).
- (EN) ISO 11737-1:2018 / A1:2021: Sterilization of health care products — Microbiological methods — Part 1: Determination of a population of microorganisms on products (fully applicable).
- (EN) ISO 14644-1:2015: Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration (fully applicable).
- (EN) ISO 14644-3:2019: Cleanrooms and associated controlled environments - Part 3: Test methods (fully applicable).
- ISO 14971:2019 / EN ISO 14971:2019/Amd 11:2021: Medical devices – Application of risk management to medical devices (fully applicable).
- (EN) ISO 15223-1:2021: Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements (fully applicable).
- (EN) ISO 17665-2024: Sterilization of health care products – Moist heat –Requirements for the development, validation and routine control of a sterilization process for medical devices (fully applicable).
- ISO 23640:2011 / EN ISO 23640:2015: In vitro diagnostic medical devices: Evaluation of stability of in vitro diagnostic reagents (Applicable with exclusion of the following sections: No standard is

available for the evaluation of stability of Medical Devices, therefore this standard is used as guideline for the set-up of the stability testing in line with the EU list of harmonized standards drafted in support of Council Directive 93/42/EEC and MDR 2017/745).

- IEC 62366-1:2015/A1:2020: Medical devices - Part 1: Application of usability engineering to medical devices (fully applicable).
- NBOG BPG 2014-3: Guidance for manufacturers and Notified Bodies on reporting of Design Changes and Changes of the Quality System (fully applicable).
- EMA/CHMP/578661/2010 rev.1: EMA recommendation on the procedural aspects and dossier requirements for the consultation to the EMA by a notified body on an ancillary medicinal substance or an ancillary human blood derivate incorporated in a medical device or active implantable medical device (fully applicable).
- MDR 2017/745: European Medical Device Regulation 2017/745 of 5 April 2017 (fully applicable).

9 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
V.1	20/09/2020	Initial version	Date: not yet Validation language: English
V.2	20/04/2023	EU Rep details	Date: not yet Validation language: English
V.3	30/06/2023	Description of accessories intended to be used in combination with the device	Date: 06/09/2023 Validation language: English This version has been approved by the Notified Body
V.4	28/12/2023	Annual update based on Clinical Evaluation Report and literature. Added vigilance section, applicable standards, and formatting updates.	Date: not yet Validation language: English
V.5	27/12/2024	Annual update. Updated references for ESHRE benchmarks.	Date: not yet Validation language: English
V.6	09/10/2025	Annual update. Updated product variant details and IFU reference to comply with MDCG 2019-9. Editorial corrections.	Date: 10th October 2025 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.

11 References

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2. 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.
3. Falah, K., H. Banna, I. Aghaways, A. Zangana and M. FL. (2014). "Using in-vitro maturation of immature oocytes retrieved from poor responder patients to improve pregnancy outcomes in Sulaimani government region, Iraq." European Scientific Journal 10(33): 195-211.
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6. Rashid, M. R., F. B. Ong, M. H. Omar, S. P. Ng, A. Nurshaireen, N. S. Sharifah-Teh, A. H. Fazilah and M. A. Zamzarina (2008). "GnRH agonist and GnRH antagonist in intracytoplasmic injection cycles." Med J Malaysia 63(2): 113-117.
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9. Ribas-Maynou, J., S. Novo, M. Torres, A. Salas-Huetos, S. Rovira, M. Antich, and M. Yeste (2022). “Sperm DNA integrity does play a crucial role for embryo development after ICSI, notably when good-quality oocytes from young donors are used. ” Biol Res, 55: 41.
10. Ribas-Maynou, J., S. Novo, A. Salas-Huetos, S. Rovira, M. Antich, and M. Yeste (2023). “Condensation and protamination of sperm chromatin affect ICSI outcomes when gametes from healthy individuals are used. ” Hum Reprod, 38: 371-86