SUMMARY OF SAFETY AND CLINICAL PERFORMANCE

10% PVP IN FERTICULT FLUSHING MEDIUM

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device. The SSCP is not intended to replace the Instructions For Use (IFU) as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to the intended users.

1 Device identification and general information

1.1 Device trade name(s)

10% PVP in FertiCult Flushing medium

1.2 Manufacturer's name and address

FertiPro NV
Industriepark Noord 32
8730 Beernem
Belgium

1.3 Manufacturer's single registration number (SRN)

BE-MF-000000313

1.4 Basic UDI-DI

5411967PVP169

1.5 Medical device nomenclature description/text

Applicable EMDN code: U08020502 (Materials/solutions for preparation/handling for assisted reproduction)

1.6 Class of device

Class III to Annex VIII of the MDR (Regulation (EU) 2017/745)

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

10% PVP in FertiCult Flushing medium: 2013

1.8 Authorised representative if applicable; name and the SRN

Not applicable

1.9 NB's name and single identification number

BSI Group The Netherlands BV
NB identification number: 2797

2 Intended use of the device

2.1 Intended purpose

10% PVP in FertiCult Flushing medium is a viscous medium containing polyvinylpyrrolidone (PVP) used for sperm preparation for Intracytoplasmic Sperm Injection (ICSI). These 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 10% PVP in FertiCult Flushing medium prior to nicking the tail to immobilize sperm completely.

2.2 Indication(s) and intended patient groups

10% PVP in FertiCult Flushing medium is a viscous medium that can be used in ICSI procedures.
Direct physical contact occurs between the media products and the human sperm cell. The medium does not come into contact with the human body.

2.3 Contraindications and/or limitations

There are no reasonably foreseeable medical conditions for which 10% PVP in FertiCult Flushing medium is not to be used.

3 Device description

3.1 Description of the device

10% PVP in FertiCult Flushing medium is a viscous medium that can be used in ICSI procedures.

10% PVP in FertiCult Flushing medium contains human serum albumin (HSA). The inclusion of HSA (which is a medicinal substance derived from human blood plasma) in assisted reproductive technology (ART) media from FertiPro is approved by the European Medicine Agency (EMA).

The device is not intended for single use. Multiple single-procedures can be performed with one bottle of 10% PVP in FertiCult Flushing medium. 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).

10% PVP in FertiCult Flushing medium 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 generation of the device has been brought on the market by FertiPro.

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

No accessories for 10% PVP in FertiCult Flushing medium are identified.

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

10% PVP in FertiCult Flushing medium can be used in combination with general ART labware and/or media. There are no specific devices that are intended to be used with 10% PVP in FertiCult Flushing medium.

4 Risks and warnings

4.1 Residual risks and undesirable effects

The output from the clinical evaluation reports of 10% PVP in FertiCult Flushing medium and/or Human Serum Albumin (HSA) are taken into account in the risk assessment report of 10% PVP in FertiCult Flushing medium in order to determine the benefits/ risk ratio.

The only remaining residual risk is the inclusion of HSA in 10% PVP in FertiCult Flushing medium. The inclusion of this medicinal substance derived from human blood plasma in the device is approved by the EMA. A potential risk associated with HSA is the transmission of viral or prion-carried diseases and the batch-to batch variation:

- **Batch-to-batch variation** is still a problem because of the inherent variability in donor blood. Due to this fluctuation, standardization of procedures remains difficult.
  - ↔ For this reason, a mouse embryo assay is routinely performed as part of the batch release criteria of HSA (incoming inspection). Furthermore, a mouse embryo assay and human sperm survival assay are routinely performed as part of media batch release criteria of 10% PVP in FertiCult Flushing medium.
- Secondly; with the use of a human-derived protein source, a potential risk exists of **transmitting viral or prion-carried diseases**.

↔ Human albumin solution is manufactured with a pasteurization procedure that has led to an excellent viral safety record over the 50 years of clinical use. 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 FertiPro ART-media.

↔ On the other hand, despite the rigorous quality controls, all cell culture media should still be treated as potentially infectious. At present, there is no known test method that can offer full assurance that products derived from human blood will not transmit infectious agents. Direct physical contact occurs between 10% PVP in FertiCult Flushing medium and the human sperm cell. The instructions for use/MSDS clearly warn that the medium contains human albumin solution and that protective clothing should be worn.

The major benefit of HSA in 10% PVP in FertiCult Flushing medium is clear:

- pH regulator
- Osmotic regulator
- Stabilizator of cell membrane
- Nutrient and carrier of growth promoting substances (i.e. amino acids, vitamins, fatty acids, hormones, growth factors)
- Scavenger (of for example toxins and waste products from cell metabolism)
- Surfactant (anti-adhesion), thereby facilitating gamete and embryo manipulation

Based on an analysis, 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 10% PVP in FertiCult Flushing medium with inclusion of HSA has been judged acceptable.

With respect to the above, following information is provided to the customer:

- Product composition is clearly indicated on the labels and instructions for use
- Instructions for use contains the following warning:
  - Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, 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. There are no reports of proven virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes. Therefore, handle all specimens as if capable of transmitting HIV or hepatitis.
  - All blood products should be treated as potentially infectious. Source material used to manufacture this product was tested and found non-reactive for HbsAg and negative for Anti-HIV-1/-2, HIV-1, HBV, and HCV. Furthermore, source material has been tested for parvovirus B19 and found to be non-elevated. No known test methods can offer assurances 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):

- Do not use the product if:
  - it becomes cloudy or shows any evidence of microbial contamination
  - seal of the container is opened or defect when the product is delivered

- expiry date has been exceeded

- Do not freeze before use
- Keep away from sunlight
- Do not re-sterilize after opening
- Depending on the number of procedures that will be performed on one day, remove the required volume of medium under aseptic conditions in an appropriate sterile recipient. This is in order to avoid multiple openings/warming cycles of the medium. Discard excess (unused) media. If multiple openings are needed, open PVP0.2S bottles via the screw cap, instead of punching the cap with a needle.
- Evaporation of the PVP solution on the slide or dish and the presence of human albumin may occasionally cause a small amount of precipitation in the medium.
- Aseptic technique should be used to avoid possible contamination.
- Always wear protective clothing when handling specimens.
- Any serious incident (as defined in European Medical Device Regulation 2017/745) that has occurred should be reported to FertiPro and the competent authority of the Member State in which the user and/or patient is established.

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

No field safety corrective actions with regard 10% PVP in FertiCult Flushing medium were needed.

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

5.1 Real-world evidence analyses

A literature search is performed to investigate whether embryological or clinical ART obtained during literature search are consistent with the outcomes as described in the benchmark papers from the ESHRE (European Society of Human Reproduction and Embryology) (see tables below).

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 competency limits concerning embryological outcomes are reported by the expert group:

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%) 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.***

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 1347 institutions in 40 countries, with a total of 918 159 treatment cycles (covering the time period from 1 January to 31 December 2016) (Wyns et al. 2020) and data is summarized in the table below.

ART in Europe, 2016: results generated from European registries by ESHRE	**Intra cytoplasmic sperm injection (ICSI) (407 222 cycles):**

(Wyns C, Bergh C, Calhaz-Jorge C, De Geyter C, Kupka MS, Motrenko T, et al. ART in Europe, 2016: results generated from European registries by ESHRE. Hum Reprod Open. 2020;2020(3):hoaa032.)	Clinical pregnancy rate per aspiration: 25% (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%) Delivery rate per transfer: 26.8% (range: 16.9 – 58.4%) ***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.***

Reported outcomes in the ESHRE papers are considered as benchmark data for ART procedures.

The articles studying the performance of 10% PVP in FertiCult Flushing medium are indicated in the table below. Overall, it can be concluded from these papers that embryological and/or clinical ART outcomes when 10% PVP in FertiCult Flushing medium is used are consistent with the embryological minimal competency limits (ESHRE Special Interest Group of Embryology 2017) and/or with the published ART outcomes as reported by the ESHRE (Wyns et al. 2020), suggesting a safe and adequate performance of 10% PVP in FertiCult Flushing medium.

Papers [1]
(Noorashikin et al. 2008)
(Rashid et al. 2008)
(Aghaways, Falah, and Ali 2016)
(Falah et al. 2014)
(Pena et al. 2018)

5.2 Device registers

In addition, clinical data is obtained from IVF centers in Europe that use 10% PVP in FertiCult Flushing 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 are consistent with the ART outcomes as described in the benchmark paper from the ESHRE.

5.3 Analysis complaint, customer/market feedback, vigilance

No additional actions were initiated, based on the cumulative nature and/or occurrence of all complaints, customer/market feedback and vigilance (if any) during the PMCF analysis.

5.4 An overall summary of the clinical performance and safety

10% PVP in FertiCult Flushing medium functions as stated by the manufacturer. This is established by clinical data, obtained during literature search, which demonstrate that embryology and ART outcomes of procedures in which 10% PVP in FertiCult Flushing medium is used are consistent with the published competency limits and/or ART outcomes as reported by the ESHRE papers, and by clinical data from IVF centers in Europe which show that ART outcomes of procedures in which 10% PVP in FertiCult Flushing medium is used are consistent with the published national ART outcomes in the country where the IVF clinic is located or with the published outcomes as reported the ESHRE.

[1] One additional article was retrieved that describe the safety and performance of 10% PVP in FertiCult Flushing medium. Due to reasons of confidentiality, this paper is not listed in the table. Note however that all outcomes in the control group described in this additional article are consistent with the outcomes as described in the benchmark papers from the ESHRE.

Moreover, there is no evidence from the clinical data, as well as from the registered complains, market/customer feedback and/or vigilance that 10% PVP in FertiCult Flushing medium is toxic for gametes, nor that the media have risk for mutagenity, oncogenicity, teratogenity, carcinogenity, cytotoxicity, allergenicity and irritancy for patients and users.

These data further suggest that the benefit risk ratio of 10% PVP in FertiCult Flushing medium remains acceptable.

5.5 Ongoing or planned post-market clinical follow-up

Post-market clinical follow-up for 10% PVP in FertiCult Flushing medium (including PMCF for the HSA component included) will be performed at least yearly and will include analyses of real-world evidence by performing a literature search, screening of device registers for clinical data, as well as analysis of all complaints, customer/market feedback, vigilance.

This Summary of Safety and Clinical Performance will be updated with information from the post-market clinical follow-up, if this is needed to ensure that any clinical and/or safety information described in this document remains correct and complete.

6 Possible diagnostic or therapeutic alternatives

Other methods for sperm selection in ICSI have been proposed (for further reading, reference is made to (Simopoulou et al. 2016)). However, despite the suggested alternatives, PVP remains the most common medium in which spermatozoa are exposed for ICSI (Simopoulou et al. 2016).

7 Suggested profile and training for users

10% PVP in FertiCult Flushing media are used in specialized laboratories performing fertilization techniques, including IVF, ICSI and sperm preparation / analysis. The intended users are assisted reproductive technologies (ART) professionals (lab technicians, embryologists and 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 2019-9**: Summary of safety and clinical performance A guide for manufacturers and notified bodies (August 2019).

The following technical standards apply to 10% PVP in FertiCult Flushing medium:

- **MDR 2017/745**: European Medical Device Regulation 2017/745 of 5 April 2017.
- **(EN) ISO 13485:2016/ EN ISO13485:2016/Ac:2018**: Medical devices — Quality management systems — Requirements for regulatory purposes.
- **ISO 10993-1:2018 /EN ISO 10993-1/2020**: Biological evaluation of medical devices -- Part 1: Evaluation and testing.
- **(EN) ISO 10993-5:2009**: Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity.
- **(EN) ISO 10993-18:2020:** Biological evaluation of medical devices – Part 18: Chemical characterization of medical device materials within a risk management process.
- **ISO 13408-1:2008 (Amd 1:2013)/EN ISO 13408-1:2015**: Aseptic processing of health care products – Part 1: general requirements.
- **(EN) ISO 13408-2:2018**: Aseptic processing of health care products – Part 2: Filtration.
- **ISO 14644-1:2015/EN ISO 14644-1:2016**: Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration.
- **(EN) ISO 14644-3:2019**: Cleanrooms and associated controlled environments - Part 3: Test methods.
- **(EN) ISO 14971:2019**: Medical devices – Application of risk management to medical devices.

- **ISO 15223-1: 2021/(EN) ISO 15223-1:2016**: Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements.
- **(EN) ISO 17665-1:2006**: Sterilization of health care products – Moist heat – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices.
- **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)
- **EN *556*-2:2015**: Sterilization of medical devices – Requirements for medical devices to be designated 'STERILE' –Requirements for aseptically processed medical devices.
- **(EN) ISO 20417:2021**: Information to be supplied by the manufacturer.
- **IEC 62366-1:2015 (Amd 1:2020)**: Medical devices - Part 1: Application of usability engineering to medical devices.
- **NBOG BPG 2014-3**: Guidance for manufacturers and Notified Bodies on reporting of Design Changes and Changes of the Quality System.
- **EMA/CHMP/578661/2010**: 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.

9 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.1	5/10/2020	Initial version	Date: not yet Validation language: English
A.2	22/07/2021	Update 2021	Date: not yet Validation language: English
A.3	20/09/2021	MDR conformity assessment review round 2	Date: not yet Validation language: English
A.4	14/12/2021	MDR conformity assessment review round 3	Version A.4 is validated by the Notified Body Validation language: English

10 Summary of the safety and clinical performance of the device intended for patients

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

11 References

Aghaways, I. H. A., K. M. Falah, and A. A. Ali. 2016. 'The difference in the outcomes between surgically retrieved and ejaculated spermatozoa for Intracytoplasmic Sperm Injection Cycles in Sulaimanyah province', *Acta Medica International*, 3: 30-38.

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.

Falah, KM., H. Banna, I. Aghaways, AR. Zangana, and Mohammad 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: 195-211.

Noorashikin, M., F. B. Ong, M. H. Omar, M. R. Zainul-Rashid, A. Z. Murad, A. Shamsir, M. A. Norsina, A. Nurshaireen, N. S. Sharifah-Teh, and A. H. Fazilah. 2008. 'Affordable ART for developing countries: a cost benefit comparison of low dose stimulation versus high dose GnRH antagonist protocol', *J Assist Reprod Genet*, 25: 297-303.

Pena, F., R. Davalos, A. Rechkemmer, A. Ascenzo, and M. Gonzales. 2018. 'Embryo development until blastocyst stage with and without renewal of single medium on day 3', *JBRA Assist Reprod*, 22: 49-51.

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: 113-7.

Simopoulou, M., L. Gkoles, P. Bakas, P. Giannelou, T. Kalampokas, K. Pantos, and M. Koutsilieris. 2016. 'Improving ICSI: A review from the spermatozoon perspective', *Syst Biol Reprod Med*, 62: 359-71.

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