Summary of Safety and Clinical Performance

FertiCult™ Flushing media

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)

- FertiCult™ Flushing medium without human albumin (alternative name in Sil-Select™ Plus kit: Sil-Select™ Plus Sperm Washing / Insemination medium without human albumin)
- FertiCult™ Flushing medium (alternative name in Sil-Select™ Plus kit: Sil-Select™ Plus Sperm Washing / Insemination medium)
- FertiCult™ Flushing medium with gentamicin (alternative name in Sil-Select™ Plus kit: Sil-Select™ Plus Sperm Washing / Insemination medium with gentamicin)
- FertiCult™ Flushing medium with phenol red (alternative name in Sil-Select™ Plus kit: Sil-Select™ Plus Sperm Washing / Insemination medium with phenol red)
- FertiCult™ Flushing medium with phenol red and gentamicin (alternative name in Sil-Select™ Plus kit: Sil-Select™ Plus Sperm Washing / Insemination medium with phenol red and gentamicin)

Remark: When FertiCult™ Flushing media are assembled in a kit together with Sil-Select™ Plus media, the products are marketed under the name "Sil-Select™ Plus Sperm Washing / Insemination media". However, this does not change anything to the content of the bottles and their intended use. So this SSCP is also applicable for "Sil-Select™ Plus Sperm Washing / Insemination media".

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

5411967FLUSH1WY

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 device according to Annex VIII of the MDR (Regulation (EU) 2017/745)

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

2012

1.8 Authorized representative if applicable; name and the SRN

Not applicable

1.9 Notified Body (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

FertiCult™ Flushing media are intended for *in vitro* procedures including washing of human gametes (sperm and oocytes), sperm swim-up procedures, intra-uterine insemination (IUI) of the spermatozoa and intracytoplasmic sperm injection (ICSI). FertiCult™ Flushing media can also be used for human embryo washing and holding, and for embryo transfer in the uterine cavity.

2.2 Indication(s) and intended patient groups

FertiCult™ Flushing media are used in specialized laboratories performing assisted fertilization technologies, including in vitro fertilization (IVF), ICSI and sperm preparation/analysis. The intended users assisted reproductive technologies (ART) professionals (lab technicians, embryologists, or medical doctors).

The red square in the figure below shows the steps in the ART process wherein FertiCult™ Flushing media can be used.

Direct physical contact occurs between the medium and human gametes/embryos. With embryo transfer and IUI, the medium comes into direct contact with the uterus mucosal membranes of the patient.

2.3 Contraindications and/or limitations

Not applicable, no contra-indications/ limitations FertiCult™ Flushing media are not to be used.

3 Device description

3.1 Description of the device

- For the principle of operation, reference is made to the IFU: FP09 I08 R01.
- FertiCult™ Flushing media are not intended for single use. Multiple single-procedures can be performed. 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).
- FertiCult™ Flushing media are sterilized using aseptic processing techniques (filtration).
- FertiCult™ Flushing medium is a HEPES-buffered medium which also contain bicarbonate, physiologic salts, glucose, lactate, pyruvate and human serum albumin[1]. The medium is also available with phenol red and/or gentamicin.
  The inclusion of HSA (which is a medicinal substance derived from human blood plasma) in ART media from FertiPro is approved by the European Medicine Agency (EMA).
  The added gentamicin (medicinal substance) complies with Ph. Eur. Monograph Standard 0331, is EDQM-certified and is approved by the Medicines Evaluation Board (MEB, the competent authority of The Netherlands).

[1] With exception of FertiCult™ Flushing medium without human albumin.

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

Not applicable, no previous generation of the devices have been brought on the market by FertiPro.

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

Not applicable, no accessories identified.

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

- For FertiCult™ Flushing medium without human albumin: FertiPro NV strongly suggests to supplement FertiCult™ Flushing medium without human albumin with 4.0 g/l human albumin solution before use.
- When Sil-Select™ Plus Sperm Washing/ Insemination media are assembled in a kit together with Sil-Select™ Plus media: Sil-Select™ Plus Upper layer and Sil-Select™ Plus Lower layer.

4 Risks and warnings

4.1 Residual risks and undesirable effects

The output from the clinical evaluation report and of the clinical evaluation outcome report of HSA and gentamicin are taken into account in the risk management file of FertiCult™ Flushing media in order to determine the benefits/risk ratio.

The only remaining residual risk is the inclusion of HSA in FertiCult™ Flushing media. The inclusion of this medicinal substance derived from human blood plasma in the devices is approved by the EMA.

The major benefit of HSA in FertiCult™ Flushing media 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

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 (MEA) is routinely performed as part of the batch release criteria of the HSA (incoming inspection). Furthermore, a MEA as well as a human sperm survival assay (HSSA) are routinely performed as part of the media batch release.
- Transmission of viral or prion-carried diseases:
  - HSA 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 FertiCult™ Flushing media and human gametes or embryos. There is no contact with the human body as these media are not intended for embryo transfer. The instructions for use/MSDS clearly warn that the medium contains human albumin solution and that protective clothing should be worn.

Based on the 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 FertiCult™ Flushing media with inclusion of HSA has been judged acceptable.

Furthermore, following information is provided to the customer:

- Product composition is clearly indicated on the labels and instructions for use
- IFU contains the following warnings:
  - 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

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

- Do not use the product if:
  - it becomes discoloured (if medium contains phenol red), 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
- Do not re-sterilize after opening
- Products that include gentamicin should not be used on a patient that has a known allergy to gentamicin or similar antibiotics
- 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.
- Keep away from (sun)light
- Aseptic technique should be used to avoid possible contamination even when the product contains gentamicin
- 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 NV 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

Not applicable, no field safety corrective actions with regard to FertiCult™ Flushing media were needed so far.

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

5.1 Real-world evidence analyses

A literature search is performed on a yearly basis, to investigate whether clinical embryology and ART outcomes obtained during the search are consistent with the clinical outcomes described in the following benchmark papers from the European Society of Human Reproduction and Embryology (ESHRE):

- Embryology outcomes:

ESHRE Special Interest Group of Embryology, 'The Vienna consensus: report of an expert meeting on the development of	ICSI normal fertilization rate:	≥65%
	IVF normal fertilization rate:	≥60%

art laboratory performance indicators', Hum Reprod Open, 2017: hox011.		

- Clinical ART outcomes:

	IVF	**ICSI**	**Frozen embryo replacement (FER):**	**IUI**
Smeenk, J., C. Wyns, C. De Geyter, M. Kupka, C. Bergh, I. Cuevas Saiz, D. De Neubourg, K. Rezabek, A. Tandler-Schneider, I. Rugescu, and V. Goossens. 2023. 'ART in Europe, 2019: results generated from European registries by ESHRE', Hum Reprod, 38(12): 2321–2338.	Clinical pregnancy rate per aspiration: **27.0%** *(range: 18.4 – 53.1%)*	Clinical pregnancy rate per aspiration: **24.9%** *(range: 16.0 – 46.1%)*	Pregnancy rate per thawing: **36.5%** *(range: 22.5 – 50.1%)*	Using husband semen (IUI-H): Delivery rate per cycle: **9.4%** *(range: 1.9 – 23.1%)*
	Clinical pregnancy rate per transfer: **38.1%** *(range: 27.4 – 63.0%)*	Clinical pregnancy rate per transfer: **37.2%** *(range: 26.9 – 52.1%)*	Pregnancy rate per transfer: **37.1%** *(range: 22.5 – 56.0%)*	
	Delivery rate per aspiration: **19.3%** *(range: 12.3 – 29.4%)*	Delivery rate per aspiration: **17.8%** *(range: 10.6 – 28.6%)*	Delivery rate per thawing: **25.8%** *(range: 7.2 – 41.4%)*	Using donor semen (IUI-D): Delivery rate per cycle: **14.3%** *(range: 6.5 – 27.9%)*
	Delivery rate per transfer: **27.6%** *(range: 17.9 – 45.9%)*	Delivery rate per transfer: **27.0%** *(range: 12.1 – 39.4%)*	Delivery rate per transfer: **26.2%** *(range: 8.4 – 42.4%)*	

The articles retrieved in literature are indicated in the table below. Overall, it can be concluded from these papers that embryological and clinical ART outcomes, when FertiCult™ Flushing media are used are consistent with the outcomes described in the benchmark papers.

Papers describing the use of FertiCult™ Flushing media ***for washing ova, spermatozoa and embryos***
Benchaib, M., J. Lornage, C. Mazoyer, H. Lejeune, B. Salle, and J. Francois Guerin. 2007. 'Sperm deoxyribonucleic acid fragmentation as a prognostic indicator of assisted reproductive technology outcome', Fertil Steril, 87: 93-100.
Frydman, N., N. Prisant, L. Hesters, R. Frydman, G. Tachdjian, P. Cohen-Bacrie, and R. Fanchin. 2008. 'Adequate ovarian follicular status does not prevent the decrease in pregnancy rates associated with high sperm DNA fragmentation', Fertil Steril, 89: 92-7.
Huang, C. C., D. P. Lin, H. M. Tsao, T. C. Cheng, C. H. Liu, and M. S. Lee. 2005. 'Sperm DNA fragmentation negatively correlates with velocity and fertilization rates but might not affect pregnancy rates', Fertil Steril, 84: 130-40
Fauque, P., P. Jouannet, C. Davy, J. Guibert, V. Viallon, S. Epelboin, J. M. Kunstmann, and C. Patrat. 2010. 'Cumulative results including obstetrical and neonatal outcome of fresh and frozen-thawed cycles in elective single versus double fresh embryo transfers', Fertil Steril, 94: 927-35.
Benchaib, M., V. Braun, D. Ressnikof, J. Lornage, P. Durand, A. Niveleau, and J. F. Guerin. 2005. 'Influence of global sperm DNA methylation on IVF results', Hum Reprod, 20: 768-73.
Le Du, A., I. J. Kadoch, N. Bourcigaux, S. Doumerc, M. C. Bourrier, N. Chevalier, R. Fanchin, R. C. Chian, G. Tachdjian, R. Frydman, and N. Frydman. 2005. 'In vitro oocyte maturation for the treatment of infertility associated with polycystic ovarian syndrome: the French experience', Hum Reprod, 20: 420-4.
Barraud-Lange, V., J. C. Pont, K. Pocate, J. M. Kunstmann, C. Chalas-Boissonas, B. Ducot, and J. P. Wolf. 2011. 'Seminal leukocytes and clinical outcomes with donor sperm insemination', Fertil Steril, 96: 1320-24 e1
Pont, J. C., C. Patrat, P. Fauque, M. L. Camp, V. Gayet, and J. P. Wolf. 2012. '[Pre-washing catheter dramatically improves the post intrauterine insemination pregnancy rate]', Gynecol Obstet Fertil, 40: 356-9.
Falah, K. M., H. Banna, I. Aghaways, A.R. Zangana, and F.L. mohammad. 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.

Desch, L., C. Bruno, C. Herbemont, F. Michel, S. Bechoua, S. Girod, P. Sagot, and P. Fauque. 2015. 'Impact on ICSI outcomes of adding 24 h of in vitro culture before testicular sperm freezing: a retrospective study', Basic Clin Androl, 25: 6.
Jansen, Chjr, Mglm Elisen, C. W. Leenstra, E. M. Kaaijk, K. J. van Stralen, and H. R. Verhoeve. 2017. 'Longer time interval between semen processing and intrauterine insemination does not affect pregnancy outcome', Fertil Steril, 108: 764-69.
Le Bras, A., L. Hesters, V. Gallot, C. Tallet, G. Tachdjian, and N. Frydman. 2017. 'Shortening gametes co-incubation time improves live birth rate for couples with a history of fragmented embryos', Syst Biol Reprod Med, 63: 331-37.
Llabador, M. A., A. Pagin, C. Lefebvre-Maunoury, F. Marcelli, B. Leroy-Martin, J. M. Rigot, and V. Mitchell. 2015. 'Congenital bilateral absence of the vas deferens: the impact of spermatogenesis quality on intracytoplasmic sperm injection outcomes in 108 men', Andrology, 3: 473-80
Philippon, M., G. Karsenty, B. Bernuz, B. Courbiere, T. Brue, J. Saias-Magnan, and J. Perrin. 2015. 'Successful pregnancies and healthy live births using frozen-thawed sperm retrieved by a new modified Hotchkiss procedure in males with retrograde ejaculation: first case series', Basic Clin Androl, 25: 5.
Fournier, C., E. Labrune, J. Lornage, G. Soignon, S. Giscard d'Estaing, J. F. Guerin, and M. Benchaib. 2018. 'The impact of histones linked to sperm chromatin on embryo development and ART outcome', Andrology, 6: 436-45.
Hachemi, M., M. Bensaada, A. Rouabah, A. Zoghmar, S. Benbouhedja, L. Rouabah, and M. Benchaib. 2019. 'Effect of Spermatic Nuclear Quality on Live Birth Rates in Intracytoplasmic Sperm Injection', J Hum Reprod Sci, 12: 122-29.
Delaroche, L., H. Caillou, F. Lamazou, E. Genauzeau, P. Meicler, P. Oger, C. Dupont, and P. Humaidan. 2021. 'Live birth after intrauterine insemination: is there an upper cut-off for the number of motile spermatozoa inseminated?', RBMO, 42: 117-24.
Mayeur, A., N. Ahdad, L. Hesters, M. Grynberg, S. Romana, C. Sonigo, and N. Frydman. 2020. 'Does the prognosis after PGT for structural rearrangement differ between female and male translocation carriers?', Reprod Biomed Online, 40: 684-92.
Puy, V., A. Mayeur, A. Levy, L. Hesters, J. Raad, S. Monnot, J. Steffann, and N. Frydman. 2020. 'CTG Expansion in the DMPK Gene: Semen Quality Assessment and Outcome of Preimplantation Genetic Diagnosis', J Clin Endocrinol Metab, 105.
Cil, N., C. Kabukcu, U. Cabus, T. Turan, and G. A. Mete. 2022. 'Retrospective comparison of the semen preparation techniques for intrauterine insemination: Swim-up versus density gradient method', J Gynecol Obstet Hum Reprod, 51: 102321.
Hachemi, M., A. Zoghmar, L. rouabah, L. Ounisa, S. Benbouhedja, M. Bensaada, and A. Rouabah. 2021. 'Impact of paternal genome with a high DNA fragmentation index (>60%) on early embryonic development', International journal of gynecological and obstetrical research, 8: 60-67.
Carles, M., E. Lefranc, D. Bosquet, S. Capelle, F. Scheffler, H. Copin, R. Cabry, and M. Benkhalifa. 2023. 'In vitro maturation of oocytes from stimulated IVF-ICSI cycles using autologous cumulus cell co-culture: A preliminary study', Morphologie, 107: 28-37
Steiner, Naama, Maryam Al Shatti, Russell Frank, Keren Rotshenker-Olshinka, Jacob Ruiter-Ligeti, and Michael H. Dahan. 2023. 'Relationship between Number of Mature Follicles and Pregnancy Rates in IUI Cycles in Women 38 to 43 Years Old', CEOG, 50.
Bouet, Pierre-Emmanuel, Mariette Bruand, Kevin Bellaïche, Bruno Vielle, Guillaume Legendre, Philippe Descamps, Romain Corroenne, Pascale May-Panloup, and Hady El Hachem. 2022. 'The role of peak serum estradiol level in the prevention of multiple pregnancies in gonadotropin stimulated intrauterine insemination cycles', Scientific Reports, 12.
Berdin, A., K. Bellaiche, H. El Hachem, B. Vielle, G. Legendre, P. Descamps, P. May-Panloup, S. Prevost, and P. E. Bouet. 2024. 'Comparison of two cancellation strategies to lower the risk of multiple pregnancies in gonadotropin stimulated intrauterine insemination cycles', Int J Gynaecol Obstet.
Mosa, Munirah Mohammed, Amsha Saud Aburasyin, Shaimaa Ahmed Aljishi, Baneen Jaffar Almurouhn, and Wesam Abdulwasea Saeed Al-Mekhlafi. 2024. 'Unlocking fertility success: A comprehensive exploration of age and intrauterine insemination outcomes', Medical Science, 28: e26ms3315.
Papers describing the use of FertiCult™ Flushing media ***for sperm injection in oocytes during ICSI***
Ledee, N., R. Lombroso, L. Lombardelli, J. Selva, S. Dubanchet, G. Chaouat, F. Frankenne, J. M. Foidart, E. Maggi, S. Romagnani, Y. Ville, and M. P. Piccinni. 2008. 'Cytokines and chemokines in follicular fluids and potential of the corresponding embryo: the role of granulocyte colony-stimulating factor', Hum Reprod, 23: 2001-9
Ledee, N., C. Munaut, V. Serazin, S. Perrier d'Hauterive, L. Lombardelli, F. Logiodice, R. Wainer, V. Gridelet, G. Chaouat, F. Frankenne, J. M. Foidart, and M. P. Piccinni. 2010. 'Performance evaluation of microbead and ELISA assays for follicular G-CSF: a non-invasive biomarker of oocyte developmental competence for embryo implantation', J Reprod Immunol, 86: 126-32.
Abbas, HH., DM. Al - Jarah, HH. Abbas, and AJ. Chiad. 2020. 'Short Agonist and Antagonist Protocols in Normoresponding Patients Undergoing ICSI, a comparative study', PJMHS, 14: 1623-31.

Papers describing the use of FertiCult™ Flushing media ***for the introduction of washed spermatozoa in the uterus (IUI)***
Barraud-Lange, V., J. C. Pont, K. Pocate, J. M. Kunstmann, C. Chalas-Boissonas, B. Ducot, and J. P. Wolf. 2011. 'Seminal leukocytes and clinical outcomes with donor sperm insemination', Fertil Steril, 96: 1320-24 e1.
Pont, J. C., C. Patrat, P. Fauque, M. L. Camp, V. Gayet, and J. P. Wolf. 2012. '[Pre-washing catheter dramatically improves the post intrauterine insemination pregnancy rate]', Gynecol Obstet Fertil, 40: 356-9.
Jansen, Chjr, Mglm Elisen, C. W. Leenstra, E. M. Kaaijk, K. J. van Stralen, and H. R. Verhoeve. 2017. 'Longer time interval between semen processing and intrauterine insemination does not affect pregnancy outcome', Fertil Steril, 108: 764-69.
Vichinsartvichai, P., S. Siriphadung, K. Traipak, P. Promrungrueng, C. Manolertthewan, and S. Ratchanon. 2015. 'The Influence of Women Age and Successfulness of Intrauterine Insemination (IUI) Cycles', J Med Assoc Thai, 98: 833-8.
Vichinsartvichai, P., K. Traipak, and C. Manolertthewan. 2018. 'Performing IUI Simultaneously with hCG Administration Does Not Compromise Pregnancy Rate: A Retrospective Cohort Study', J Reprod Infertil, 19: 26-31.
Ruiter-Ligeti, J., M. H. Dahan, N. Steiner, A. Volodarsky-Perel, and W. Buckett. 2020. 'Is intrauterine insemination a viable treatment option for women over 43 years old? An analysis by ovarian stimulation protocol and sperm source', J Assist Reprod Genet, 37: 3103-07.
Papers describing the use of FertiCult™ Flushing media ***for the preparation of density gradient***
El Khattabi, L., C. Dupont, N. Sermondade, J. N. Hugues, C. Poncelet, R. Porcher, I. Cedrin-Durnerin, R. Levy, and C. Sifer. 2013. 'Is intracytoplasmic morphologically selected sperm injection effective in patients with infertility related to teratozoospermia or repeated implantation failure?', Fertil Steril, 100: 62-8.
Papers describing the use of FertiCult™ Flushing media ***for washing ova, spermatozoa and embryos AND for the preparation of density gradient***
Dupont, C., E. Hafhouf, N. Sermondade, O. Sellam, C. Herbemont, J. Boujenah, C. Faure, R. Levy, C. Poncelet, J. N. Hugues, I. Cedrin-Durnerin, C. Sonigo, M. Grynberg, and C. Sifer. 2015. 'Delivery rates after elective single cryopreserved embryo transfer related to embryo survival', Eur J Obstet Gynecol Reprod Biol, 188: 6-11.
Sifer, C., L. El Khattabi, C. Dupont, N. Sermondade, C. Herbemont, R. Porcher, I. Cedrin-Durnerin, C. Faure, R. Levy, M. Grynberg, C. Poncelet, and J. N. Hugues. 2014. 'Could sperm grade under high magnification condition predict IMSI clinical outcome?', Eur J Obstet Gynecol Reprod Biol, 181: 189-94.
Herbemont, C., S. Sarandi, J. Boujenah, I. Cedrin-Durnerin, N. Sermondade, A. Vivot, C. Poncelet, M. Grynberg, and C. Sifer. 2017. 'Should we consider day-2 and day-3 embryo morphology before day-5 transfer when blastocysts reach a similar good quality?', Reprod Biomed Online, 35: 521-28.
Vichinsartvichai, P., S. Siriphadung, K. Traipak, P. Promrungrueng, C. Manolertthewan, and S. Ratchanon. 2015. 'The Influence of Women Age and Successfulness of Intrauterine Insemination (IUI) Cycles', J Med Assoc Thai, 98: 833-8.
Vichinsartvichai, P., K. Traipak, and C. Manolertthewan. 2018. 'Performing IUI Simultaneously with hCG Administration Does Not Compromise Pregnancy Rate: A Retrospective Cohort Study', J Reprod Infertil, 19: 26-31.
Gonzalez-Ravina, C., E. Santamaria-Lopez, A. Pacheco, J. Ramos, F. Carranza, L. Murria, A. Ortiz-Vallecillo, and M. Fernandez-Sanchez. 2022. 'Effect of Sperm Selection by Magnetic-Activated Cell Sorting in D-IUI: A Randomized Control Trial', Cells, 11.
Jamil, M., H. Debbarh, A. Kabit, M. Ennaji, L. Koumba, I. Kaarouch, M. Zarqaoui, W. R. Senhaji, E. M. Hissane, B. Saadani, P. Vanderzwalmen, N. Louanjli, and R. Cadi. 2023. 'Comparison between density gradient centrifugation method, an extended version of the horizontal swim up method and the combination of both for sperm selection', Obstet Gynecol Sci, 66: 221-29.
Papers describing the use of FertiCult™ Flushing media ***for other purposes***
Buffat, C., C. Patrat, F. Merlet, J. Guibert, S. Epelboin, N. Thiounn, A. Vieillefond, A. Adda-Lievin, C. Lebon, and P. Jouannet. 2006. 'ICSI outcomes in obstructive azoospermia: influence of the origin of surgically retrieved spermatozoa and the cause of obstruction', Hum Reprod, 21: 1018-24.
Parmegiani, L., G. E. Cognigni, S. Bernardi, E. Troilo, S. Taraborrelli, A. Arnone, A. M. Maccarini, and M. Filicori. 2012. 'Comparison of two ready-to-use systems designed for sperm-hyaluronic acid binding selection before intracytoplasmic sperm injection: PICSI vs. Sperm Slow: a prospective, randomized trial', Fertility and Sterility, 98: 632-37.
Beauvillard, D., A. Perrin, H. Drapier, C. Ravel, T. Freour, C. Ferec, M. De Braekeleer, and V. Amice. 2015. '[Congenital bilateral absence of vas deferens: From diagnosis to assisted reproductive techniques - the experience of three centers]', Gynecol Obstet Fertil, 43: 367-74.
Wijdan A.Taha, Hayder A. L. Mossa Layla J. Hussein. 2022. 'Relationship Between Sperm Hyaluronan Binding Assay And Sperm Preparation Techniques In A Sample Of Iraqi Infertile Couples', Journal of Pharmaceutical Negative Results: 1308-12.

5.2 Device registers

Clinical data is obtained from IVF clinics in Europe and South-Africa (with a total of 24 661 cycles) that use FertiCult™ Flushing media. The reported embryological and/or clinical ART outcomes of all clinics are consistent with the outcomes described in the above mentioned benchmark papers, or with published national ART outcomes in the country where the IVF clinic is located.

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

FertiCult™ Flushing media functions as stated by the manufacturer: i.e. FertiCult™ Flushing media supports *in vitro* procedures involving human gametes (sperm and oocytes), including washing of gametes, sperm swim-up procedures, IUI of the spermatozoa and ICSI. FertiCult™ Flushing media can also be used for human embryo washing and holding, and for embryo transfer in the uterine cavity.

This is established by clinical data obtained during literature search and from IVF centers which demonstrate that embryological outcomes and clinical ART outcomes of procedures in which FertiCult™ Flushing media were used are consistent with the published outcomes as reported by the Vienna consensus group and the ESHRE, or are consistent with published national ART outcomes in the country where the IVF clinic is located.

Furthermore, there is no evidence from the clinical data, as well as from the registered complains, market/customer feedback and/or vigilance that FertiCult™ Flushing media is toxic for gametes and embryos, nor that the media have no risk for mutagenity, oncogenicity, teratogenity, carcinogenity, cytotoxicity, allergenicity and irritancy for patients and users. No infrequent complications or problems were detected.

5.5 Ongoing or planned PMS/PMCF

PMS/PMCF for FertiCult™ Flushing media (including PMCF for the HSA and gentamicin component included in FertiCult™ Flushing media) will be performed at least yearly and will include analyses of real-world evidence by performing literature search, screening of device registers for clinical data, as well as analysis of all complaints, customer/market feedback and vigilance.

This SSCP will be updated with information from PMS/PMCF, 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

Several devices as FertiCult™ Flushing media with a similar intended use are available on the European Union or international markets. Besides these media, there are no other alternative treatments that can be used.

7 Suggested profile and training for users

FertiCult™ Flushing media are used in specialized laboratories performing assisted fertilization technologies, including IVF, ICSI and sperm preparation/analysis. The intended users are ART 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 technical standards apply to FertiCult™ Flushing media:

ISO 13485:2016 EN ISO 13485:2016 (Amd 11:2021)	Medical devices — Quality management systems — Requirements for regulatory purposes.
MDR 2017/745	European Medical Device Regulation 2017/745 of 5 April 2017
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

ISO 14971:2019 EN ISO 14971:2019 (Amd 11:2021)	Medical devices – Application of risk management to medical devices
(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
(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.
(EN) ISO 11737-1:2018, A1:2021	Sterilization of health care products - Microbiological methods - Part 1: Determination of a population of microorganisms on products
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
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
(EN) ISO 13408-6:2021	Aseptic processing of health care products – Part 6: Isolator systems
(EN) ISO 14644-1:2015	Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness
(EN) ISO 14644-3:2019	Cleanrooms and associated controlled environments - Part 3: Test methods
ISO 10993-1:2018 EN ISO 10993-1:2020	Biological evaluation of medical devices – Part 1: Evaluation and testing
(EN) ISO 10993-3:2014	Biological evaluation of medical devices -- Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.
(EN) ISO 10993-5:2009	Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity.
ISO 10993-9:2019 EN ISO 10993-9:2021	Biological evaluation of medical devices -- Part 9: Framework for identification and quantification of potential degradation products.
(EN) ISO 10993-10:2023	Biological evaluation of medical devices -- Part 10: Tests for irritation and skin sensitization.
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
(EN) ISO 10993-23:2021	Biological evaluation of medical devices – Part 23: Tests for irritation
(EN) ISO 22442-1: 2020	Medical Devices utilizing animal tissues and their derivatives: Part 1: Application of risk management
Ph. Eur. 331	European Pharmacopoeia monograph 331 – Gentamicin sulfate
Ph. Eur. 0255	European Pharmacopoeia monograph 0255 – Human albumin solution

9 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.2	22/09/2020	Initial validated version	Version A.2 is validated by the Notified Body Validation language: English
A.3	05/07/2021	Update 2021: addition PMCF data	Not submitted for validation, as there were no significant changes that required validation.
A.4	14/06/2022	Update 2022: addition PMCF data	Not submitted for validation, as there were no significant changes that required validation.
A.5	05/07/2023	Update 2023: addition PMCF data	Not submitted for validation, as there were no significant changes that required validation.

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.6	13/06/2024	Update 2024: addition of PMCF data	Not submitted for validation, as there were no significant changes that required validation.