Summary of Safety and Clinical Performance

Product name PureSperm™ Wash

The following information is intended for users/healthcare professionals.

Contents

1. Device identification and general information

1.1. Device trade name

PureSperm™ Wash

1.2. Manufacturer's name and address

PureSperm Wash (PSW) is manufactured at Nidacon production facility in Mölndal, Göteborg and at APL Umeå production facility.

- APL Umeå Formvägen 5B, 906 21 Umeå, Sweden
- Nidacon International AB Flöjelbergsgatan 16 B, 431 37 Mölndal, Sweden

Product	Size (ml)	Cat.No	Nidacon	APL
PSW100	100	PSW-100		X
PSW020	20 ml x 2	PSW-020	X	
PSW006	6 ml x 20	PSW-006	X	

1.3. Manufacturer's single registration number (SRN)

SE-MF-000001933

1.4. Basic UDI-DI

7350025610077P

1.5. Medical device nomenclature description / text

EMDN (CND) code is U08 Gynaecological Devices and U0802 Assisted Reproduction Devices

1.6. Class of device

Europe: 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

- PSW 100, CE cleared for PSW100 in 2017-02-07.
- PSW020 was released in 2008, CE cleared for PSW020 2019-12-11.
- PSW006 was added to the Class III certificate 2019-12-11 as included in PureSperm SpeediKit. Will now be sold separately as PSW006, 6 ml x 20.

1.8. Authorised representative if applicable, name and the SRN

Not applicable

1.9. NB's name (the NB that will validate the SSCP) and the NB's single identification number

The British Standards Institution (BSI),

Nb Identification number: 2797

2. Intended use of the device

2.1. Intended purpose

For washing the sperm pellet recovered from a PureSperm density gradient, for use in the swim-up method and for extending semen, or sperm pellet for use in IUI.

2.2. Indication(s) and target population(s)

Indication is infertility, unable to conceive. Infertile couples are the target group. This target population consists of adults. No anatomical location can be specified.

A couple is classified as infertile (primary infertility) when according to WHO's definition, they have actively been trying to conceive for 24 months. Secondary infertility is when earlier pregnancies have occurred, could be abortions or spontaneous miscarriages. About 4-10 % of all couples have secondary infertility and 3-6% has primary infertility.

2.3. Contraindications and/or limitations Medical Device Medical Device Coordination Group

There are now reasonably foreseeable medical conditions for which PureSperm Wash are not to be used.

3. Device description

3.1. Description of the device

The overall design of PSW is based on the transition of sperm from the ejaculate into the environment of the egg. The pH and osmolality are higher in the ejaculate than in the uterus and, therefore these variables decrease in the system. The pH and osmolality in the gradient system are lower than in the ejaculate and higher than in PSW. The composition of PureSperm Wash has been carefully balanced to optimise sperm survival while avoiding ionic shock. The pH and osmotic values are set to lie intermediately between those in the semen (liquefied ejaculate, pH 7.8, ~340 mOsmol), from where the sperm cells originate, and those in the fertilisation medium (pH 7.35, 285 mOsmol), where the sperm are placed after washing for fertilisation of the oocyte.

3.2. A reference to previous generations

Year	Product	Description of design change	Reason for change
2002	ReadySwim, SpermAssist and PureSperm Wash	All are gathered into one product (PureSperm Wash) and the supplier of hSA is changed	No need for three products with same composition
2011	PSW 100 and PSW0202	New hSA from Octapharma instead of Baxter	No longer made available for OEM

2017	PSW100	CE mark is to be added in all material (however not for PSW-020)	PureSperm Wash 100 mL is CE marked
2020	PSW020	Update of all documentation	PSW-020 is CE marked
2023	PSW 006	PSW006 and PS80 are now separate products and not both in PureSpermSpeedikit.	Dividing the two products enables an easier access to the European market

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

- Bench top centrifuge with swing out rotor.
- Disposable sterile conical or round bottomed centrifuge tubes
- Sterile pipette
- Disposable sterile round bottomed centrifuge tubes
- CO2 incubator

3.4. Description of any other devices and products which are intended to be used in combination with the device Intended use. CER of the product in question.

Devices from Nidacon used in combination with PSW.

- PureSperm 40/80/90, which are ready-to-use gradients for density gradient preparations prior to the washing step with PureSperm Wash.
- PureSperm 100 which a stock solution to prepare density gradient layers from prior to a density gradient preparation and the washing step with PureSperm Wash.
- PureSperm Buffer which is a salt solution used to dilute the stock solution PureSperm 100 to the different layers for the density gradient preparation prior to the washing step with PureSperm Wash.

PureSperm 40/80/90/100 Clinical Evaluation Report TEF 00475

PureSpermBuffer Clinical Evaluation report TEF 00544

4. Risks and warnings

4.1. Residual risks and undesirable effects

Identified hazard	Description of hazard
Infectious agents in hSA	Virus transmission with albumin derived from human
Birth defects	Birth defect seen in children born after IVF

4.2. Warnings and precautions

Precautions and Warnings as noted in instructions for use (IFU)

- Use aseptic procedures at all times
- If available, use sealed buckets during centrifugation to avoid creation of aerosols
- PureSperm Wash does not represent any fire or combustion hazard. A safety data sheet is available from the distributor or manufacturer (see www.nidacon.com)
- Do not use any PureSperm Wash which shows evidence of bacterial contamination
- Do not use contents if tamper evident seal is broken, sterile packaging damaged or if stopper accidently comes in contact with unsterile surfaces
- Do not re-use PureSperm Wash from any procedure due to risk for cross contamination
- Federal Law (USA) restricts this device to sale by or on the order of a physician on US markets, not applicable in EU
- Please check for regulatory compliance governing the use of ART products in your country
- No known indication of toxic, allergic sensitivity or any pathological effects
- Notice: If any serious incident has occurred in relation to the device this should immediately be reported to the manufacturer and the competent authority of the Member State in which the user and/or patient is established.

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.

It is strongly recommended that every time PureSperm Wash is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.3. Other relevant aspects of safety, including a summary of any field safety corrective action (FSCA including FSN) if applicable.

There has been no need for a preventive and/or corrective action for PureSperm Wash. Competent authorities and notified body have not been notified. No adverse events have been found to be relevant for PureSperm Wash.

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

5.1. Summary of clinical data related to equivalent device, if applicable

Not applicable, no equivalent products

5.2. Summary of clinical data from conducted investigations of the device before the CE-marking, if applicable

Shelf-life studies were performed and comparison tests with a similar device. Similar in the context of being used clinically in the same way.

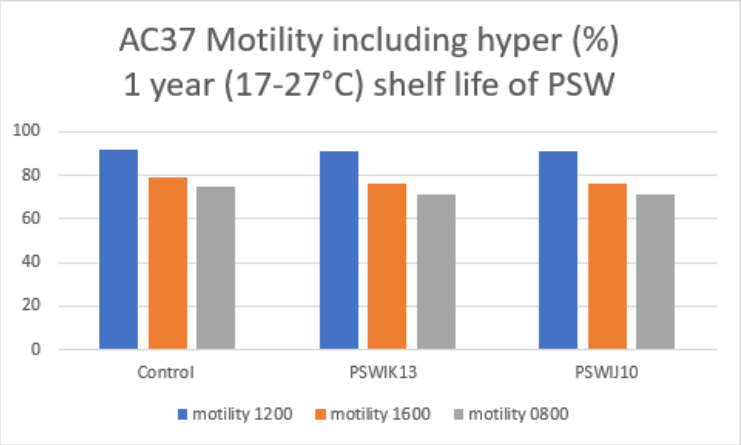
Initial study – shelf life

PSW was released in year 2000 with shelf-life for 12 months in RT (real time), room temperature (15-30˚ C according to standard room temperatures considering all climate zones). In the initial stability

study batch PSWGF15 was stored at 40 C for three months (June-August) according to accelerated method (Arrhenius, ¼ of the expected). Sterility was confirmed and the following comment is included “the yield and motility of sperm prepared using the incubator wash were comparable to the control (room temperature) wash. Yields were 20.04 and 19,7 x 106 for incubator and room temperature washes respectively, while motilities were 91% and 93% respectively”.

Follow-up second study

The results from RT 2002-05-07 at 30˚C in incubator 1 year (see results below). The pH value and osmolality comply.



Second follow-up study

Purpose of study: New stability studies were initiated in 2017, completed in 2022.The plan was needed to further clarify our stability study results in the stability report.
No plans to extend the shelf-life from the set 12 months from previously. This real time study is mainly performed to prove the already confirmed shelf-life but with the storage temperature of 30°C throughout the shelf-life and add chemical characterization.

Design of experiment: Same test laboratories as used for batch releases was used. Laboratories that have been used for an extended period.

Conclusion of stability test: Physical parameters such as pH and Osmolality also stay within an acceptable range. Measurements of components at production and after one year show deviations in some concentrations but it is concluded that the product is functional and safe regardless of this fact. PSW stays clear and without precipitation after 1 year in required storage conditions. Integrity of packaging is not tested by other means than sterility measurements and experience from being shipped across the world for almost two decades with no incidents reported. Sterility and low endotoxin level is maintained throughout the storage period of 1 year. Biological tests have shown acceptable results, even after storage in extreme temperatures and after opening bottles several times during the storage period. Biological tests with sperm (HSSA) prove its effectiveness after one year in storage in different temperatures and after opening when stored in refrigerator.

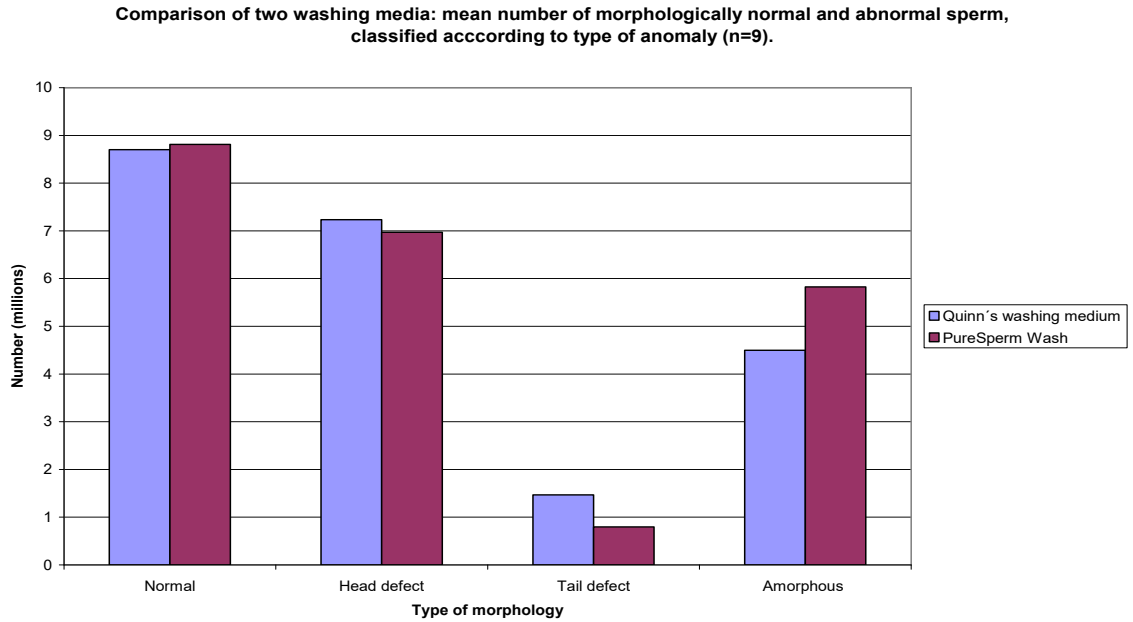
Bench-top study performed at Nidacon

Comparative Study performed at Nidacon 2004

Purpose of Study: To determine the numbers and the morphology of sperm retrieved after a standard density-gradient separation from semen and followed by a washing step in one of two washing media, Quinn’s Washing Medium compared with Nidacon’s PureSpermWash medium.

Design of Experiment: Each donation of human semen is divided into two parts, one for the Quinn's Washing Medium and the other for the PureSpermWash medium, the split-ejaculate technique. Normal sperm are separated from donor semen utilising a standard, density-gradient centrifugation technique. Subsequently, a sperm pellet resulting from the centrifugation is transferred to another centrifugation tube containing one of two washing media, wherein the pellet is firstly dispersed and then re-centrifuged. The numbers and the morphology of retrieved sperm were determined using computer assisted sperm analyser (CASA) after the washing step, whereby the efficacy of Quinn's Washing Medium could be compared with that of PureSpermWash.

Results:



Conclusions: From the graphical illustration above comparing PureSperm Wash with Quinn's Washing Medium for the preparation of human sperm, it is quite clear that the two media are quite comparable and exhibit almost identical efficacy for the final washing of human sperm, subsequent to their density gradient separation. This research work was carried out in the reproduction research laboratories of Nidacon International AB, in Mölndal, Sweden. The sperm in this work were prepared from donor semen and were not subsequently used in any patient treatment.

SpeediKit - Performance testing at Nidacon of preparation of human sperm on a single layer

Purpose of study: To compare a single layer preparation to a regular density gradient preparation. The study was performed at Nidacon.

Design of Experiment: Aliquots (1.5 mL) of ejaculates were prepared on a single layer of PureSperm colloid (4 mL), by centrifugation at 300 x g for 30 minutes. The sperm pellet was transferred to PureSperm Wash (6 mL) for washing by centrifugation at 500 x g for 10 minutes.
The sperm pellet was re-suspended in PureSperm Wash and the motility and viability were assessed at three time points by both subjective motility analysis and by computerized analysis using the IVOS (Hamilton Thorne). The sperm preparations were kept at room temperature (approximately 22°C) for 18 hrs. The resulting sperm preparations (figure 1) contained a mean of approximately 90% motile sperm immediately after preparation with at least 70% sperm remaining viable after 18 hrs. after preparation.

These sperm preparations were considered to be equivalent to density gradient preparations in terms of yield of motile sperm.

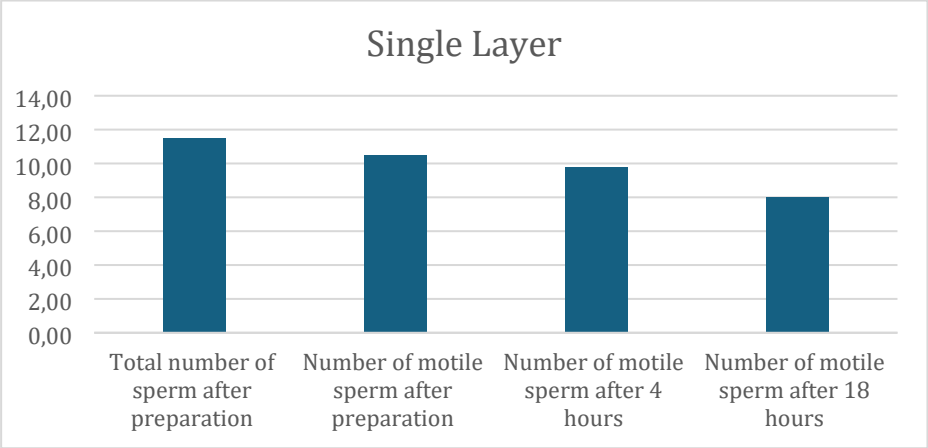


Figure 1: Single layer preparation of sperm: total yield and number of motile sperm at three time points (mill/ml)

Comparison with double layer gradients:
Aliquots of human sperm were prepared by the (i) single layer technique and (ii) double layer (PureSperm 40 and 80) technique. Due to the higher density in the upper two mL in the single layer tubes, centrifugation time was 10 minutes longer than for the double layer tubes. A similar yield of motile sperm was obtained from the preparations in both types of techniques (figure 2). Motility was the same.

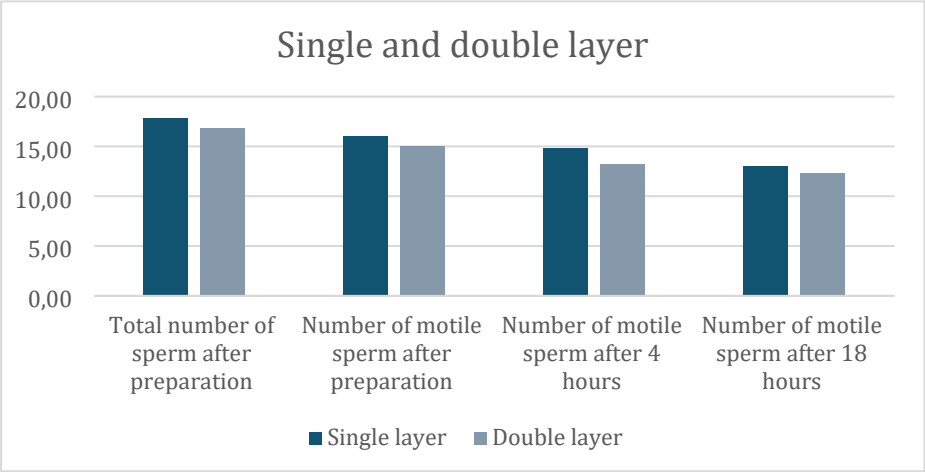


Figure 2: Comparison of total yield and number of motile sperm using single- and double-layer centrifugation techniques (mill/ml)

Conclusions from the two tests performed at Nidacon using human sperm on single layer

- The single layer preparation method offers a convenient and rapid method of processing sperm for IUI.
- The use of single layer preparation method gives comparable yield as with double layer density gradient preparation method.
- The use of 6 ml prefilled tubes with PSW is convenient and safe to use.

5.3. Summary of clinical data from other sources, if applicable

Performance testing – Clinical overview:

Clinic data post release that has been collected from national registries, reference clinics or published data using PureSperm Wash. Track record from the QC testing of PSW is also included.
The clinical benefits of using PureSperm Wash for washing of the pellet will be verified, showing safety and performance factors, track record of QC tests performed will verify a safe production and stable product. Multiple factors are involved in an IVF treatment and PureSperm Wash is a small part in the process. Some studies are therefore included to verify that PSW does not compromise the final result of the treatment.

QC tests
Track record for all batches updated after each PMS meeting every year.

International/National registries Q-IVF
About 30 years ago, each IVF clinic in Sweden started sending annual summaries to the Swedish National Board of Health and Welfare. In the mid-90s, permission was obtained from the Data Inspectorate to establish an individual-based register containing all IVF treatments that led to childbirth. The aim of Q-IVF is to monitor treatment results and identify potential risks for men and women who have undergone IVF-treatment as well as children born as a result of IVF. The registry likewise is a valuable data source for clinics to benchmark their development and qualitative work, as well as being a base for scientific research.

The positive experiences from the individual-based register led to the start of the Q-IVF Quality Register in 2007, and now all reporting is done there. This register is run jointly by all IVF clinics in Sweden. Q-IVF is therefore one of the most complete IVF-registers in the world. It includes reports for clinics all together and individually and can therefore be used to gather results from clinics using the PureSperm Wash in their daily routine.

Due to high numbers of cycles, being both public and private data, IVF clinics with state-of-the-art methods (for example one embryo per transfer) and data that has been collected consistently for a long period of time, the data is considered very reliable. It will be real world evidence on PureSperm Wash since the data represents the entire population in Sweden, it is non-comparative and does not involve experimental exposure.

ESHRE
Each year, the European Monitoring Consortium (EIM) for ESHRE publishes a peer-reviewed report, which collects, analyses and reports ART data generated in Europe. The European IVF Monitoring Programme (EIM) was established to collect, process and finally publish regional data for Europe on direct clinical results and side-effects, follow-up children's well-being and also the availability and the structure of services in the different countries.

Published data in Scientific literature on PSW
Literature search for comparative published studies using the product or studies where the patient treatments are reported is performed in line with PMS process for Nidacon. This search on the product will verify the usability, safety and efficacy of the product. Performed to evaluate the benefit-risk profile and verifying that the risks that are handled in the AEA of the PureSperm Wash are relevant and that no new risks have arisen. The risk analysis includes every step of the recommended stages for use and shall be compared to the current state of the art. The search defines context and endpoints in the safety and performance assessments.

All studies divided into the different categories.

No	Study	Data source	Performance	Safety
	QC test			
Post-9	Track record of QC testing after production	Nidacon	X	X
	Registry data			
Post-4	2015-17 Registry data Clinical data on deliveries per transfer	Q-IVF Swedish national registry	X	X
Post-7	Registry data - Clinical results from 2019	Q-IVF Swedish national registry	X	X
Post-8	Registry data - Clinical results from 2018-01-01-2020-06-30	Q-IVF Swedish national registry	X	X
Post-10	Registry ESHRE IUI data 2018	ESHRE European registry	X	X
Post-12	Registry data - Clinical results from 2019-01-01-2021-06-30	Q-IVF Swedish national registry	X	X
Post-13	Registry data - Clinical results from 2022	Q-IVF Swedish national registry	X	X
	Results from publications			
Post-1	2004 IUI using PSW	Atlanta, US	X	X
Post-2	2014 Comparison with Irvine wash media	Tripler Army Center Honolulu, US	X	X
Post-3	2014 Sperm viability and capacitation	Univ of Padova	X	
Post-5	2013-17 Clinical data	Biologia cellular, Spain	X	X
Post-6	2020 Clinical data	Reproductive medicine, Italy	X	X

Post- 1 Study using PureSperm Wash for intra uterine insemination (IUI) 2004

Roudebush, W. E., Toledo, A. A., Kort, H. I., Mitchell-Leef, D., Elsner, C. W., & Massey, J. B. (2004). Platelet-activating factor significantly enhances intrauterine insemination pregnancy rates in non-male factor infertility. Fertility and sterility, 82(1), 52–56. https://doi.org/10.1016/j.fertnstert.2003.11.057

Purpose of study: To determine the efficacy of treating sperm with platelet activating factor (PAF) in PureSperm Wash before IUI.

Design of experiment: Prospective randomized double-blind study of sperm for patients with a history of undergoing IUI.110 patients in (PAF) group.

Results: There was a significant difference in IUI pregnancy rates per cycle between control (10/56 17.9%) and PAF + PureSperm Wash (14/47 29,8%) treatment groups in the normal male study arm. There was also a significant difference in overall cumulative IUI pregnancy rate between control (21/81 25, 9%) and PAF+PSW (27/64 42, 2%) patient groups.

Conclusion: This study was mainly conducted to investigate the effect of platelet activating factor on the pregnancy rate when used in IUI, but it also shows that PureSperm Wash can contribute to a good pregnancy rate when used for IUI.

Post-2 Effects of Lubricants and Wash Solutions on Semen Evaluation in a Fertility Clinic Laboratory

Abadie, J. M., & Lambert, H. B. (2014). Effects of lubricants and wash solutions on semen evaluation in a fertility clinic laboratory. *Laboratory medicine*, *45*(2), 116–119. https://doi.org/10.1309/lm0rxldulfif9tq6

Purpose of study: The mail goal was to optimize and improve the quality and utility of the semen analysis report.

Method: two different gradient products and associated washing buffer was used on split semen samples. Samples incubated in wash medium were evaluated for different parameters.

Results: Composite table showing differences between count and motility over time.

	Time=0		**Time=2**	
Type of medium	Count (mill/ml)	Motility (%)	Count (mill/ml)	Motility (%)
PureSperm Wash (Nidacon)	37.9	83.8	24.9	83.6
SpermWashMedium (Irvine)	37.4	77.9	15.2	75.4

Gradient counts and motilities of the samples prior to incubation time (0) and the changes in count and motility after incubation time (2h).

Conclusion: When comparing wash media, at 2 hours PureSperm Wash was significantly higher in both motility and count compared to Irvine culture media. Shows high performance and safety for PSW.

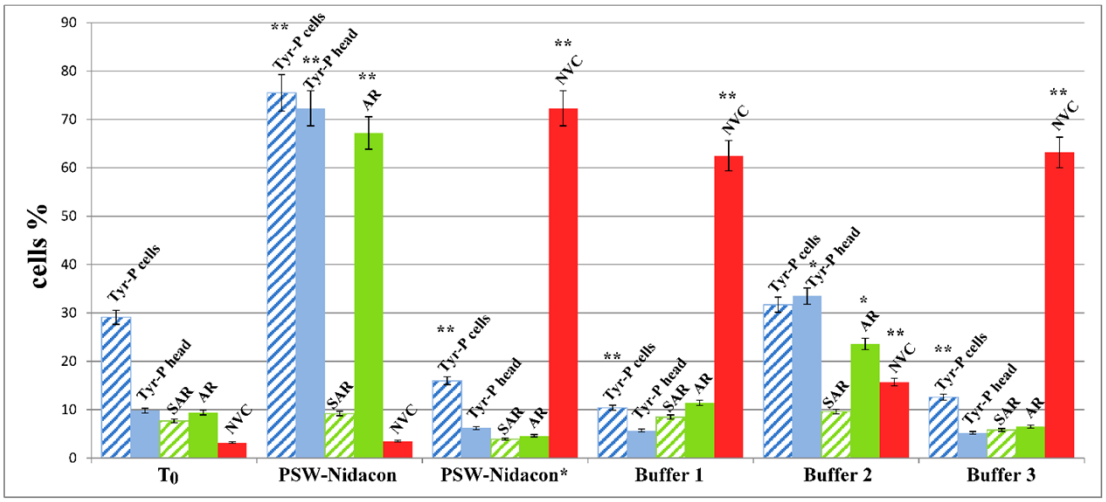
Post -3 Effect of various commercial buffers on sperm viability and capacitation 2014 (D11)

Andrisani, A., Donà, G., Ambrosini, G., Bonanni, G., Bragadin, M., Cosmi, E., Clari, G., Armanini, D., & Bordin, L. (2014). Effect of various commercial buffers on sperm viability and capacitation. *Systems biology in reproductive medicine*, *60*(4), 239–244. https://doi.org/10.3109/19396368.2014.904952

Purpose of study: A study in 2014 compared the effect of different commercial buffers according to their capacity to induce reactive oxygen species (ROS) production, the tyrosine phosphorylation (Tyr-P) of the head and consequently, acrosome reaction (AR), paying particular attention to the cell survival at the end of 2h incubation. The study was performed at Department of Molecular Medicine at University of Padova, Italy.

Design of experiment: Sperm from 48 donors, incubated for 180 min in capacitating conditions in different buffers, were analysed for Tyr-P pattern, AR and viability (NVC) by immunofluorescence cytochemistry. Number of cells expressed as % of the total amount of cells showing Tyr-P in any part of the cell-body, or in the head, were detected and reported as Tyr-P cells and Tyr-P head, respectively. Percentage of cells undergoing acrosome reaction or not viable cells (AR and NVC, respectively) was also reported.
Spontaneous AR percentages were also evaluated in each sample in the absence of A23187 and values reported (SAR).

Results: PureSperm Wash was by far the best medium for sperm preparation: in fact, cells reaching the AR (67.2±7.9%) were almost three-five-fold compared with results obtained with other commercial buffers. PSW also preserved cells from apoptosis (only 3.5±1.4% of total cells were not viable) compared with the great number observed with the other ones.



Sperm biochemical parameters observed with different buffers.Sperm, incubated for 180 min in capacitating conditions in different buffers were analysed.

The study also addressed the well-known problem on how buffers must be stored, since human serum albumin, glucose, lactate etc. promote bacterial/fungal contamination, thus resulting in increased buffer ROS production with a consequent fast sperm denaturation and inability to reach the capacitated state. Capacitation implies marked reorganization of membrane architecture, due to the activity of extracellular proteins which have the task of extracting cholesterol and reorganizing membrane in specialized microdomains, also called rafts, capable of remodelling and reorganizing themselves to undergo acrosome reaction. Once capacitation has occurred, these rafts migrate from the flagellum, where they are found extensively, to the peri-acrosomal region where they presumably allow interaction with the oocyte. The buffers used in the ART for sperm preparation must induce optimal conditions to achieve AR, an, once more, PSW clearly showed the best membrane reorganization to achieve the potential AR.

PureSperm Wash is an optimal sperm medium to prepare sperm to undergo the potential successive AR and to prevent time-dependent denaturation.

Post-4 Deliveries after IVF – Clinical results Sweden 2015-2017

Published in Q-IVF-report 2019

The report used in this clinical evaluation consists of all started treatments in Sweden during 2015-2017 from all clinics, both private and public. Many clinics in Sweden have been using PSW for a longer period and we have therefore used the results from the above-mentioned register to demonstrate the results for use of PSW. The table below is a part of the yearly report, presenting data from deliveries from 2015-2017.

Number of transfers for each clinic, using PSW. A total number of 6651 transfers reported.

Age group	Akademiska Uppsala	RMC Malmö	Linköping	Örebro	LIVIO Malmö	LIVIO Umeå
< 30	369	830	530	225	81	380
31-35	465	811	465	199	185	385
36-37	158	291	142	65	74	115

>37	169	292	146	91	62	121
Total no of transfers	1161	2224	1283	580	402	1001

Percentage of deliveries from fresh embryo transfer using patient gametes in different age groups from all clinics in Sweden using PureSpermWash. Riket is average result from all clinics in Sweden to which the result can be compared.

Conclusion: Using PSW does not compromise the results for an IVF clinic. The clinics using PSW are performing comparable to the average result.

Post-5 2013-17 Clinical data Barcelona, Spain

Martínez, M., Durban, M., Santaló, J., Rodríguez, A., & Vassena, R. (2021). Assisted oocyte activation effects on the morphokinetic pattern of derived embryos. Journal of assisted reproduction and genetics, 38(2), 531–537. https://doi.org/10.1007/s10815-020-02025-9

Design of study: Treatment results from a private IVF centre in Barcelona were analysed. Retrospective cohort study from 25 ICSI cycles performed between 2013 and 2017. ICSI cycles were performed from 7 ICSIs using assisted oocyte activation (AOA) and 18 normal ICSIs. PSW was used for washing after gradient preparation of the sperm sample. Morphokinetic variation was assessed using time-lapse.

Results:

	ICSI AOA	**ICSI**
Average age of male	42,8 ±8.8 years	
Average age of female	24.8±2.4 years	
Number of patients	7	18
Embryo transfer day 3 (%)	71.4	83.3
Embryo transfer day 5 (%)	28.5	16.6
Clinical pregnancy (%)	28.6	44.4

Conclusion: The ionomycin mediated AOA does not seem to affect the general morphokinetic pattern of preimplantation embryo development even though clinical pregnancy rate was lower.
The results were not compromised using PSW.

Post-6 Clinical data 2020

Zacà, C., Coticchio, G., Tarozzi, N., Nadalini, M., Lagalla, C., Garolla, A., & Borini, A. (2020). Sperm count affects cumulative birth rate of assisted reproduction cycles in relation to ovarian response. Journal of assisted reproduction and genetics, 37(7), 1653–1659. https://doi.org/10.1007/s10815-020-01807-5

Design of study: Retrospective study carried out in a private IVF centre. 750 couples diagnosed with male factor were analysed to investigate the possible influence of sperm quality, as assessed by prewash total sperm count (TSC), on cumulative success rates in assisted reproduction cycles. PSW was used for the washing of the gradient preparation.

TSC x 10^6	**Total**	**<0.1**	**0.1-1**	**1-5**	**6-10**	**11-36**	**P**
Number of patients	765	189	144	150	103	179	0.75

Mean no of retrieved oocytes	10.1	10.4	9.3	10.5	10.1	9.6	0.185
No of cumulative births %	31	22.2	27.1	34.7	36.9	36.9	0.01

Conclusion: Higher TSC values have a positive impact on cumulative success rates in cycles characterised by few (1-5) retrieved oocytes while it does not influence the outcome of cycles with a normal (6-10) or high (> 10) number of retrieved oocytes.
The results were not compromised using PSW.

Post-7. Results from Q-IVF Swedish national registry 2019
Published in Q-IVF-report 2021

Report published 2021 and includes all treatments started during 2019 in Sweden in both private and public hospitals. Starting 2020 a regularly transfer of data from IVF clinics to the registry is performed.

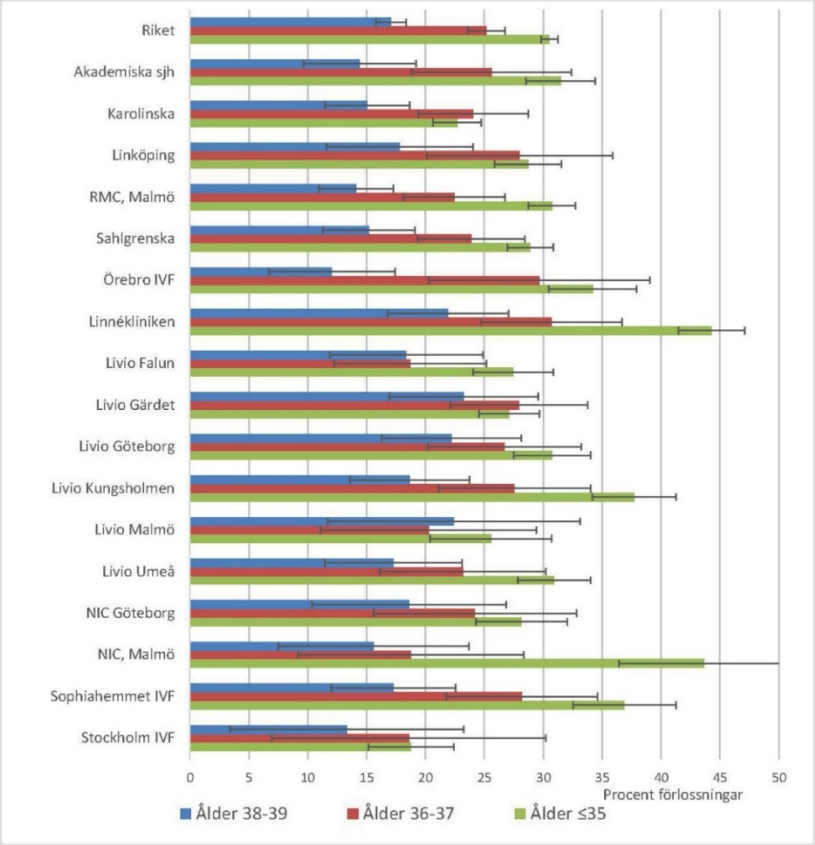
IVF using own gametes, conclusion of treatments made in 2019. All clinics were during this period using PureSperm products for all sperm preparations.

	ST.IVF	**ICSI**	**Fresh IVF in total**	**Frozen cycles**	**Total fresh and frozen**
No of cycles	5668	5425	11 093	7314	18 407
No of aspirations	5349	5072	10 421		
No of transfers	4003	3788	7791	7091	14 882
No of clinical pregnancies	1409	1287	2696	2940	5636
% Clinical pregnancies	35.2	34.0	34.6	41.5	37.9

Conclusion: Since Sweden during this period was a market where all clinics were using PSW for sperm preparations it was possible to use the concluding results for all clinics in Sweden. Of the 11 093 started treatments, 2260 resulted in a birth, that is a fifth of every started IVF treatment. The official registry has concluded that IVF is a safe and effective treatment.

Shows that PSW does not compromise the results for an IVF treatment. It is safe and high performing. Acceptable benefit-risk ratio.

Post-8 Swedish national registry Q-IVF 2022
Published in Q-IVF-report 2022



PureSpermWash is used by almost all clinics in Sweden. The graph from Q-IVF shows the result of number of deliveries from all clinics in Sweden both private and public, from treatments using own gametes between 2018-01-01-2020-06-30.

Conclusion: Since Sweden during this period was a market where all clinics were using PSW for sperm preparations it was possible to use the concluding results for all clinics in Sweden. Of the 16 712 started treatments, 4212 resulted in a birth, that is a quarter of every started IVF treatment. The official registry has concluded that IVF is a safe and effective treatment. Shows that PSW does not compromise the results for an IVF treatment. It is safe and high performing. Acceptable benefit-risk ratio.

Post-9 Track record QC tests for PSW-100

Each PureSperm Wash batch is tested biologically using only normal human semen samples. Osmolality and pH are checked on each batch after production.

The samples for biological test are separated into two parts, the one part being used for control and the second part being used for preparing sperm with the PureSperm Wash test batch. The test-batch results are compared with the results from the control. The analyses provide a count of the sperm per mL, the sperm activity is graded, and the activity is also expressed as a percentage of the total sperm. All data are recorded from before and after the separation and purification, and are compared to the control, i.e. using an earlier, already approved PureSperm Wash batch.

pH: is measured and adjusted accordingly during production and measured again just prior to testing it in the laboratory with a bench top Mettler Toledo pH meter. A sample of 1mL is added to a microcentrifuge tube and then the electrode is inserted into the sample and analysed.

Osmolality: is measured on every batch produced, by Freeze-point depression, during production and just prior to being used for testing in the laboratory. A sample of 100µL is added to a microcentrifuge tube and then added to the Osmometer and analysed.

Sperm motility: is analysed by examining a fresh wet preparation of the semen sample in a microscope under phase contrast objective. The percentage of motile sperm, non-motile sperm, non-progressively motile sperm, and hyper motile sperm is counted. The requirement for a batch release is that the normal motility is ≥80%.

Sperm survival (viability): is analysed by Computer Assisted Sperm Analysis (CASA), Hamilton Thorne (www.hamiltonthorne.com) IVOS version 12.3D (Build 002) by placing a fresh wet sample in a pre-mounted slide. The CASA will analyse the sample and give results for, among other things, the viability. The sample is analysed directly after the DGC and again after 18 hrs. The requirement is a viability of >70% after 18 hrs.

The data will be continuously updated after each PMS meeting, starting 23/24 meeting in May 2024.

Result: All batches are in the correct range for osmolality and pH, no batch outside the set range. The requirement for percentage motile sperm, set by Nidacon, is ≥ 80% motile sperm after washing. Not one batch has been close to not being rejected due to a low percentage of motile sperm. Almost all batches have been above benchmark value of 90%. The requirement for survival after 18 h is 70%, also set by Nidacon and included in QC certificate for each batch. No batch has been lower that 70%.

Conclusion: PureSperm Wash live up to and meet the design and performance requirements set in the design verification plan. From the bench tests of this products, it is evident that it is very stable and reliable in its performance.

This data ensures a stable product, no impact on safety and performance.

Post-10 ART in Europe 2018, IUI results from European registries by ESHRE

European IVF Monitoring Consortium (EIM), for the European Society of Human Reproduction and Embryology (ESHRE) , Wyns, C., De Geyter, C., Calhaz-Jorge, C., Kupka, M. S., Motrenko, T., Smeenk, J., Bergh, C., Tandler-Schneider, A., Rugescu, I. A., & Goossens, V. (2022). ART in Europe, 2018: results generated from European registries by ESHRE. Human reproduction open, 2022(3), hoac022. https://doi.org/10.1093/hropen/hoac022

Each year, ESHRE publishes a peer-reviewed report, which collects, analyses and reports ART data generated in Europe. The most recent report includes data from 1 007 598 treatment cycles (covering the period from 1st of January to 31st of December 2018) (Wyns et al 2022) provided either by national registries based on initiative of medical associations and scientific organisations or committed persons of 30 countries. It includes data on Inseminations using donated sperm from all clinics in Sweden and sine all were using PureSperm Wash during this time, data will be used for safety assurance for the IUI procedure.

Number of treatments, pregnancies, babies and deliveries, IUI-D in Sweden 2018

	Insemination with donated sperm
No of cycles	2120

No of deliveries	329
% deliveries/insemination	15.5

Conclusion: The average delivery in Europe for IUI using donated sperm was 12.6 and for Sweden 15.5. the data from ESHRE publications is considered as a benchmark and therefore the higher figure for Sweden indicates that using PureSperm Wash for IUI will not compromise the result.

Post-11 Similar product - Comparison of the effect of different media on the clinical outcome of the density gradient centrifugation/swim-up and swim-up methods

Kim, E. K., Kim, E. H., Kim, E. A., Lee, K. A., Shin, J. E., & Kwon, H. (2015). Comparison of the effect of different media on the clinical outcomes of the density-gradient centrifugation/swim-up and swim-up methods. *Clinical and experimental reproductive medicine*, *42*(1), 22–29. https://doi.org/10.5653/cerm.2015.42.1.22

Purpose of study: To determine the most optimal sperm preparation method for IVF. The Irvine product Sperm Washing Medium was used for the study. The study was performed at Fertility Center, CHA Bundang Medical Center, Seongnam, Korea.
Design of experiment: Fresh IVF cycles from Nov. 2012- March 2013 included, in total 429 cycles. Both gradient and swim-up method used for comparison.
Results: No significant differences among the groups of different preparation methods. The sperm washing medium from Irvine used for all groups as washing medium resulted in a high number of motile sperm between 97-100 % motile sperm.
Conclusion: Irvine Sperm washing Medium is included in CER as a similar medium to PureSpermWash. In the study gave a high number of motile sperm after preparation regardless of method.

Post-12 Swedish National Registry Q-IVF 2023 results treatments

Published in Q-IVF-report 2023

During the period reported 2019-01-01 – 2021-06-30 all the clinics were using PureSperm Wash.

Results for IVF treatment:

Age	**<35**		**36-37**		**38-39**		**Total**		
	No of Asp.	No of Del.	No of Asp.	No of Del.	No of Asp.	No of Del.	No of Asp.	No of Del.	Percentage
Sweden	12 951	4645	2624	748	3519	656	**19 094**	**6049**	**31.7%**

No of Asp – Number of aspirations, No of Del. – number of deliveries

Results for Insemination (IUI):

Donar insemination- IUI-D		
Started cycles	2214	
No if IUI	1916	
Positive pregn. test	400	
Delivery/IUI	311/1916	16.2%

Data from inseminations using donated sperm, majority prepared using PSW.

Conclusion: The percentage of deliveries per transfer for clinics in Sweden is above the set benchmark valued for Europe according to the ESHRE report. The reported results from inseminations using donor sperm are also above the ESHRE data for Europe, 16.2 compared to 12.6 for Europe.

The use of PureSperm Wash does not compromise the results from the clinic.

Post-13 Swedish National Registry Q-IVF 2024 results treatments
Published in Q-IVF-report 2024

A majority of the clinics are using density gradient preparation with PS-products and PSW for sperm preparation.

Results:

Number of treatments, pregnancies, birth rates per treatment type. Own gametes.

	ST IVF	ICSI	TOTAL	Percentage
Started cycles	5120	5695	10 815	
Embryo transfer	3240	3366	6606	
Positive pregnancy test	1239	1295	2534	
Pregnancy rate per transfer %				38.4
Delivery number	857	935	1778	
Delivery rate per transfer				26.9

Data from inseminations using donated sperm performed in 2022, majority prepared using PSW as washing medium.

Donor insemination- IUI-D		
Started cycles	1925	
No if IUI	1722	
Positive pregn. test	332	
Delivery/IUI	249/1722	14.5%

Benchmark values - ESHRE Registry
ART in Europe, 2018: results generated from European registries by ESHRE.
C Wyn et al Human reproduction 2022

Performance indicator	**Range**	**Benchmark** (Competence value)
Pregnancy rate per transfer %	21.1-50.5	35.9
Delivery rate per transfer	14.2-38.7	26.4
IUI – delivery rate per insemination	3.3-31.6	8.9 husband 12.6 donor

Conclusion: The percentage of pregnancy rate and deliveries per transfer for clinics in Sweden is above the set benchmark valued for Europe according to the ESHRE report. The reported results from inseminations using donor sperm are also above the ESHRE data for Europe, 14.5 compared to 12.6 for Europe.

The use of PSW does not compromise the results from the clinic.

Conclusion/Analysis for PMCF studies

No	Study	Clinic	No of patients/cycles	Main outcome
Post-1	2004 IUI using PSW	Atlanta, US	110	High pregnancy rate
Post-2	2014 comparison to Irvine wash media	Triple army Center, US	20	Higher in both motility and count compared to Irvine culture media.
Post-3	2014 Sperm viability and capacitation	Univ of Padova	48 (no transfers)	Optimal sperm medium
Post-4	2015-17 Clinical data on deliveries per transfer	National registry Sweden Q-IVF	6 651	High pregnancy rate
Post-5	2013-17 Clinical data	Biologia Cellular, Spain	25	High pregnancy rate
Post-6	2020 Clinical data	Reproductive medicine, Italy	765	High pregnancy rate
Post-7	2019 Clinical data	National registry Sweden Q-IVF	18 407	High pregnancy rate
Post-8	2018-20 Clinical data	National registry Sweden Q-IVF	16 712	High pregnancy rate
Post-9	Track record of QC tests	Nidacon	Tests on 84 batches	Stable product
Post-10	2018 IUI data	ESHRE European registry	2120	Delivery rate over EU average level
Post-11	205 Similar product data	Clin. Exp. Reprod. Med. 2015	429	High percentage of motile sperm after preparation.
Post-12	2019-2021 Clinical data	National registry Sweden Q-IVF	19 094 + 1916	Delivery rate over EU average level for both IVF and IUI
Post-13	2022 Clinical data	National registry Sweden Q-IVF	10 815 + 1925	Delivery rate over EU average level for both IVF and IUI
TOTAL			**79 037**	

Discussion regarding clinical safety, performance and side-effects:
The results from registries, different studies/clinics show a clinical safety and high performance looking at fertilisation and pregnancy rates for both IVF and IUI. Results from in total 79 037 patients show meaningful, measurable, patient-relevant clinical results. The track record for QC tests ensures a stable product. A result from a similar product, Irvine sperm washing medium also confirms high percentage of motile sperm after washing of density gradient preparation.

The number of patients included and the high quality of the clinical data address that the qualitative and quantitative aspects of clinical safety are fulfilled. The intended clinical benefits are achieved. No undesirable side-effects detected.

5.4. An overall summary of the clinical performance and safety

No	Study	Clinic	No of patients	Performance	Safety
Post-1	2004 IUI using PSW	Atlanta, US	110	X	X
Post-3	2014 Sperm viability and capacitation	Univ of Padova	48	X	X
Post-4	2015-17 Clinical data on deliveries per transfer	National registry Sweden Q-IVF	6651	X	X
D 21	Assisted oocyte activation effects on the morphokinetic pattern of derived embryos	Unit of Andrology and reproductive medicine, Padova Italy	25	X	X
D 22	Sperm count affects cumulative birth rate of assisted reproduction cycles in relation to ovarian response	Unit of Andrology and reproductive medicine, Padova Italy	765	X	
Post-7	2017-19 Clinical data on deliveries per transfer	National registry Sweden Q-IVF	18 407	X	X
Post-8	2018-20 Clinical data on deliveries per transfer	National registry Sweden Q-IVF	16 712	X	X
Post-10	Clinical data Sweden IUI 2018	ESHRE collected registry data	2120	X	X
Post-12	2019-2021 Clinical data on IVF and IUI	National registry Sweden Q-IVF	19 094+1916	X	X
Post-13	2022 Clinical data; IVF & IUI	National registry Sweden Q-IVF	10 815 + 1925	X	X
	Total no of patients		**78 588**		

The IVF process is a rather extended process in which PSW plays a limited role. The clinical performance of PureSperm Wash can however does not compromise the outcome of the treatment and will lead to clinical benefits for the patient. The benefits shown in the clinical studies is a high fertilisation rate and a high pregnancy rate when PSW is used in IVF.

For use as a washing medium after density gradient centrifugation and as a media used for swim-up PureSperm Wash is a safe and reliable product to use for the clinics. It is a well-established technique, used in IVF for many years, safe and high performing.

IVF as a method is still considered as a safe method, no new data showing differently has been found.

PureSperm Wash does not give rise to any possible risks to the mother or to any birth deformities as we are aware of today. Several clinics worldwide have used the product and no reports have been filed regarding risks to the mother or child and through a state of art literature search regarding follow-up of IVF children and parents a continuous control of any reported events is handled. This also includes the MAUDE controls for all similar products**.**

No known indication of toxic, allergic sensitivity or any pathological effects.

No side-effects detected by using PureSperm Wash as washing media/diluent or swim-up media. None of performed clinical studies using PureSperm Wash have demonstrated any side-effects.

Establishment of intended use/claims for the product PureSperm Wash

Intended use	**Verification data**
For washing the sperm pellet recovered from a PureSperm density gradient	Post-2 Comparative data Honolulu, US Post-4, 7,8,12 and 13 Data from national registry Q-IVF Sweden Post-5 clinical data Barcelona, Spain Post-6 clinical data Padova, Italy Post-9 Track record from QC tests Post-11 Motility using similar product
Use in the swim-up method	Post-3 Effect of various commercial buffers on sperm viability and capacitation (D11)
For extending semen, or sperm pellet for use in IUI	Post-1 PSW for IUI 2004 (D2) Post-9 Track record from QC tests Post-10 ESHRE report 2018 Post-12 Q-IVF Sweden 2023 Post-13 Q-IVF Sweden 2024
Claims	**Verification data**
12 months shelf life, stable pH	Bench top shelf-life studies Nidacon
Storage at 2-27°C	Bench top shelf-life studies Nidacon
No addition of antibiotics	No incident reports regarding growth in PSW

PureSperm Wash functions as stated by manufacturer: i.e. PureSperm Wash supports in vitro procedures involving human gametes (sperm) including washing, swim-up and IUI.
This is established by clinical data obtained from literature search, clinical data from reference clinics and /or national registries. This data demonstrates that embryology and /or ART outcomes of procedures in which PureSperm Wash is used, are consistent with the competence limits reported by the Vienna consensus group (ESHRE Special interest Group of Embryology 2017) and/or with the published ART outcomes reported by ESHRE (Wyns et al 2022).
Moreover, there is no evidence from the clinical data, as well as from registered complaints, market/customer feedback and/or vigilance that PureSperm Wash is toxic for gametes and embryos. Furthermore, no infrequent complications or problems were detected.

5.5. Ongoing or planned post-market clinical follow-up

Post Market Follow Up Plan for PureSperm Wash will be performed yearly and will include analyses of real-world evidence by performing literature search, screening of device registries for clinical data as well as analysis of complaints, customer feedback and vigilance.

The 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

There are several different methods for separating sperm from the seminal plasma, these include methods using different techniques. The most common are different types of migration techniques and density gradient centrifugation.
However, for the purpose of recovering the great majority of spermatozoa after a density centrifugation washing with a medium is the only solution. There are no alternative treatments that can be used instead of washing, only different media from different manufacturers.
It is not recommended to not prepare semen at all since this potentially can introduce pathogens from the seminal plasma into the uterine cavity of the woman during an IUI or expose the oocyte to pathogens during IVF and ICSI.

7. Suggested profile and training for users

The instruction for use of the PureSperm Wash is provided in the Instructions for use (IFU), product manual and on our website. The instructions are clear and easy to follow. PureSperm Wash is easy to use and a safe product. Intended to be used by qualified, professional clinical personnel trained in the techniques used in a sperm and IVF-lab.

The Intended User has requirements for qualifications stated in Directive 2004/23/EC (-on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells). There must be a designated “Responsible person” with for instance the following qualifications:

- possession of a diploma, certificate, or other evidence of formal qualifications in the field of medical or biological sciences awarded on completion of a university course of study or a course recognized as equivalent by the Member state concerned.
- have at least two years practical experience in the relevant field.

The person designated shall be responsible for the following, among other responsibilities:

- ensuring that human tissues and cells intended for human applications in the establishment for which that person is responsible are procured, tested, processed, stored, and distributed in accordance with this directive.

Personnel directly involved in activities relating to the procurement, processing, preservation, storage and distribution of tissues and cells in a tissue establishment shall be qualified to perform such tasks and shall be provided with training.

The Intended User is trained for their responsibilities.

All tissue establishments where activities of testing, processing, preservation, storage or distribution of human tissues and cells intended for human applications are undertaken have been accredited, designated, authorized, or licensed by a competent authority for the purpose of those activities.

8. Reference to any harmonised standards and CS applied

MEDDEV 2.7.1 rev 4, EN-ISO 14971:2020, Manual on borderline and classification in the Community regulatory framework for medical devices, Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices. Demonstrates conformity with General Safety and performance

requirements (GSPR) Annex 1 of MDR 2017/745. This SSCP has applied recent guidance documents, harmonized standards and common specifications.

Harmonised standards to apply, if applicable:

Standard/Version	Title
EN ISO 13485:2016 + AC:2018	Medical Devices – Quality management systems – Requirements for regulatory purposes
MDR (EU) 2017/745	European Medical Device Regulation EU-MDR Regulation (EU) 2017/745
EN ISO 10993-1:2020	Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process (ISO 10993-1:2018, including corrected version 2018-11)
EN ISO 10993-3:2014	Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
EN ISO 10993-5:2009	Tests for in vitro cytotoxicity
EN ISO 10993-10:2023	Biological evaluation of medical devices – Part 10 Tests for irritation and skin sensitization
EN ISO 10993-23:2021	Tests for irritation
EN ISO 14155:2020	Clinical investigation of medical devices for human subjects – Good clinical practice
MEDDEV 2.7.1:2016 Rev 4	Clinical Evaluation: Guide for manufacturers and notified bodies
MEDDEV 2.12:2012/2 rev 2	Post market clinical follow-up studies
EN ISO 14971:2020 (2019)	Medical Devices – Application of risk management to medical devices
MEDDEV 2.12/1:2013 Rev 8	Guidelines on a medical device vigilance system
SS-EN ISO 20417:2021	Medical devices – Information to be supplied by the manufacturer
SS-EN ISO 556-2:2024	Sterilization of medical devices – Requirements for medical devices to be designated “STERILE” – Part 2: Requirements for aseptically processed medical devices
SS-EN ISO 15223-1:2021	Medical Devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements
ISO 13408-1:2023	Aseptic Processing of health care products – Part 1: General requirements
SS-EN ISO 13408-2:2018	Aseptic processing of health care products – Part 2: Filtration
SS-EN ISO 11737-1:2018	Sterilization of health care products – Microbiological methods – Part 1: Determination of a population of microorganisms on products
SS-EN ISO 11737-1:2018/A1:2021	Sterilization of health care products – Microbiological methods – Part 1: Determination of a population of microorganisms on products – Amendment 1
SS-EN ISO 11737-2:2020	Sterilization of health care products – Microbiological methods – Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process

SS-EN ISO 14937:2009	Sterilization of health care products – General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices
SS-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
SS-EN ISO 20857:2013	Sterilization of health care products – Dry Heat – Requirements for the development, validation and routine control of sterilization process for medical devices
IEC 62366-1:2015+AMD1:2020 CSV	Medical devices – Part 1: Application of usability engineering to medical devices

List of applicable common specifications
2022-10-05 None relevant for PureSperm Wash
2023-05-02 None relevant for PureSperm Wash
2024-01-24 A new common specification has been issued covering devices detected and/or quantifying HIV and is not applicable for PureSperm Wash
2025-02-10 No new common specifications have been published that are relevant for PureSperm Wash
2026-02-12 No new common specifications have been published that are relevant for PureSperm Wash

List of applicable relevant MDCG:s:
MDCG 2019-9 - Rev.1 - Summary of safety and clinical performance A guide for manufacturers and notified bodies. March 2022.
MDCG 2020-6 Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC A guide for manufacturers and notified bodies. April 2020

Others:

Version	Title
Sixth Edition 2021	WHO laboratory manual for the Examination and processing of human semen
2016 Mortimer and Mortimer 2015	ESHRE Guideline Group on Good Practice in IVF Lab et al

9. Revision history

SSCP revision number	Date issued/changed	Change description	Revision validated by the Notified Body
12	2026-05-29	Change of NB information. No further impact.	
11	2026-05-05	Change the storage temp to 2-27 degrees C. No further impact.	
10	2026-02-13	Updated harmonised standards	

9	2025-12-18	Update after PMS 24/25	
8	2025-01-24	Update after PMS 23/24	
7	2024-04-02	Update after LoF 4	
6	2024-01-03	PSSK change	
5	2023-06-21	check for clinical reply 3	
4	2023-04-17	Update PMS 21/22	
3	2022-11-10	Update MDR	
2	2022-10-21	New version	
1	2022-10-19	First report created	Date: Language: