Summary of Safety and Clinical Performance (SSCP)

Device group: Densiron®
Devices: Densiron® 68 and Densiron® Xtra
in accordance with REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.

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 as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.

The following information is intended for users/healthcare professionals.

1. Device identification and general information

1.1. Device trade name(s)

Densiron® 68 and Densiron® Xtra

1.2. Manufacturer's name and address

Fluoron® GmbH
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Magirus-Deutz-Straße 10
89077 Ulm
Germany
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1.3. Manufacturer's single registration number (SRN)

DE-MF-000009235

1.4. Basic UDI-DI

4260160455035K

1.5. Medical device nomenclature description / text

CND Q02030202, OPHTHALMIC SURGERY, SILICONE OILS
GMDN 45125, Retinal tamponade medium, postoperative

The medical devices Densiron® 68 and Densiron® Xtra are colourless, homogenous liquids that are composed of a mixture of ultrapure polydimethylsiloxane with the formula $(CH_3)_3SiO$-$[Si(CH_3)_2O]n$-$Si(CH_3)_3$ and ultrapure perfluorohexyloctane ($C_6F_{13}C_8H_{17}$).

1.6. Class of device

The product group heavy silicone oil consists of surgically invasive medical devices that are used as postoperative long-term endotamponades in the field of ophthalmic surgery and are classified as class IIb products.

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

Product	Year
Densiron® 68	2003
Densiron® Xtra	2015

1.8. Authorised representative if applicable; name and the SRN

DE-MF-000009235

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

BSI Netherlands
Say Building, John M. Keynesplein 9
1066 EP Amsterdam, Netherlands
Identification Number of the Notified Body: 2797

2. Intended use of the device

2.1. Intended purpose

Densiron® 68/Densiron® Xtra are sterile medical devices composed of a mixture of ultrapure silicone oil (polydimethylsiloxane) and an ultrapure, semifluorinated alkane (perfluorohexyloctane). Densiron® 68/Densiron® Xtra are used as postoperative long-term endotamponades in the field of ophthalmic surgery.

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

Densiron® 68/Densiron® Xtra are intended only for ocular application. Densiron® 68/ Densiron® Xtra are used for the treatment of severe cases of retinal detachment, especially for:

- Inferior and posterior retinal holes
- Retinal detachments with giant tears
- Retinal detachments with proliferative vitreoretinopathy (PVR)
- Traumatic retinal detachments.

Densiron® 68 and Densiron® Xtra are also used as a tamponade in macular hole surgery.

Intended patient population: Patients requiring surgical treatment of severe retinal detachment or surgical treatment of a macular hole. Use in pregnant women, nursing mothers, and children is not recommended.

2.3. Contraindications and/or limitations

Densiron® 68 / Densiron® Xtra are not permitted to be used in patients that are hypersensitive to silicone oil and perfluorohexyloctane or wear a silicone intraocular lens (IOL). Because their density is greater than 1000 kg/m^3, Densiron® 68 / Densiron® Xtra are not permitted to be used in cases of superior retinal detachment. In addition, laser coagulation and cryotherapy are not permitted on eyes filled with Densiron® 68 / Densiron® Xtra.

3. Device description

3.1. Description of the device

The medical devices Densiron® 68 and Densiron® Xtra are sterile colourless, homogenous liquids that are composed of a mixture of ultrapure polydimethylsiloxane (also known as silicone oil) with the formula $(CH_3)_3SiO\text{-}[Si(CH_3)_2O]n\text{-}Si(CH_3)_3$ and ultrapure perfluorohexyloctane ($C_6F_{13}C_8H_{17}$, the so called F6H8®). They contain no biologically active components, are chemically and physiologically inert, and non-toxic. Densiron® 68 and Densiron® Xtra differ only with regard to the silicone oil: Densiron® 68 contains Siluron® 5000 and Densiron® Xtra contains Siluron® Xtra (both medical devices by Fluoron GmbH).

Densiron® 68 and Densiron® Xtra are heavier than water and are used as long-term tamponades for the treatment of severe cases of retinal detachment, especially for inferior and posterior retinal holes, retinal detachments with giant tears, retinal detachments with proliferative vitreoretinopathy (PVR) or traumatic retinal detachments.
Densiron® 68 and Densiron® Xtra are also used as a tamponade in macular hole surgery.

For this purpose, the medical device is injected into the vitreous cavity of the eye for invasive surgical applications in accordance with its intended use. With the exception of eyes having a complex baseline situation, the indwelling time for Densiron® 68 / Densiron® Xtra should be kept as short as possible and limited to at most 3 months. A short length of indwelling time can reduce potential side effects and complications.

Densiron® 68 and Densiron® Xtra are well-established medical devices. Densiron® 68 was CE certified in November 2003. Densiron® Xtra has been approved in 2015 and is marketed since then.

Densiron® Xtra is a further development of Densiron® 68.

Further, the lower viscosity of Densiron® Xtra leads to shorter injection times compared to Densiron® 68, and a higher resistance to emulsification.

Medical device	Densiron® 68	Densiron® Xtra
Composition, Chemical description	30.5% Perfluorohexyloctane (F6H8®) ($C_6F_{13}C_8H_{17}$; CAS: 133331-77-8) 69.5% Polydimethylsiloxane 5000 cSt ($(C_2H_6OSi)_n$; CAS: 63148-62-9)	30.5% Perfluorohexyloctane (F6H8®) ($C_6F_{13}C_8H_{17}$; CAS: 133331-77-8) 69.5% Polydimethylsiloxane 4200 cSt ($(C_2H_6OSi)_n$; CAS: 63148-62-9)
Density (kg/m^3) at 35 ± 2C°	1030 – 1060	
Dynamic viscosity (mPas) at 35 ± 2C°	900 – 1400	900 – 1300
Refractive index (35 ± 2C°)	1.378 - 1.388 (589 ± 10nm)	
Dosage form	The sterile medical devices Densiron® 68 and Densiron® Xtra are available in 10-mL glass vials and glass syringes. Vials and syringes are only intended for single use on one patient.	
Sterilisation method	Dry heat sterilization for the product and steam sterilisation for the packaging.	
Other informations	The medical devices Densiron® 68 and Densiron® Xtra do not contain any medical substance or derivatives of human blood or plasma. The medical devices Densiron® 68 and Densiron® Xtra do not contain tissue(s) or cells of human or animal origin or their derivatives. The medical devices Densiron® 68 and Densiron® Xtra do not contain substances or combinations of substances that are absorbed by or locally dispersed in the human body. The medical devices Densiron® 68 and Densiron® Xtra do not contain CMR (carcinogenic, mutagenic or toxic to reproduction) substances or endocrine-disrupting substances.	

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

There is no predecessor device to Densiron® 68. However, Densiron® Xtra was introduced later to the market in order to provide shorter injection times and lower emulsification rates.

Product	Variants
Densiron® 68	30.5% Perfluorohexyloctane (F6H8®) 69.5% Polydimethylsiloxane 5000 cSt
Densiron® Xtra	30.5% Perfluorohexyloctane (F6H8®) 69.5% Polydimethylsiloxane 4200 cSt

No major changes have been made to Densiron® 68 and Densiron® Xtra medical devices since their CE mark registration, respectively.

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

No specific accessories are necessary for the application of Densiron® 68/Densiron® Xtra according to its intended use.

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

The medical devices Densiron® 68/Densiron® Xtra are not intended for use in conjunction with other medical devices, medicines, or other medical technologies.

4. Risks and warnings

4.1. Residual risks and undesirable effects

Side effects / complications associated with vitrectomy together with the application of Densiron® 68 / Densiron® Xtra and identified via clinical literature data (resulted from a systematic review of scientific literature) and via complaints reported the Fluoron GmbH in context of Densiron® device application are described in the following:

Side effects and complications	**Expected frequency**	**Time of occurrence (intraoperative, postoperative)**
Anterior eye segment complications (e.g., cataract, keratopathy, corneal opacification)	> 1 of 1000	postoperative
Decrease in visual acuity to vision loss (e.g., central vein occlusion)	> 1 of 1000000 and ≤ 1 of 100000	postoperative
Emulsification (e.g., dispersion / emulsification)	> 1 of 1000	postoperative
Decreased or increased intraocular pressure (e.g., raised IOP, Hypotony, (secondary angle-closure) glaucoma)	> 1 of 1000	postoperative
Retinal re-detachment (e.g., recurrent RD, postoperative break)	> 1 of 10000 and ≤ 1 of 1000	postoperative
Intraocular inflammations	> 1 of 1000	postoperative
New membrane formation (e.g., new membrane formation, ERM)	> 1 of 10000 and ≤ 1 of 1000	postoperative
Choroidal detachment*	> 1 of 1000000 and ≤ 1 of 100000*	postoperative

*Only data on the similar device Oxane Hd are available, i.e. there are no clinical data on the product Densiron® 68 / Xtra.

All the risks (side effects / complications) described in the table above occurred during performance of vitrectomy together with the application of Densiron® 68 and Densiron® Xtra. Further, all these risks are

listed in the instructions for use of the Densiron® devices to adequately inform the ophthalmic surgeon about them. Simultaneously, all these risks of table above were also confirmed by state-of-the-art data, which are researched in context of the clinical evaluation report of the Densiron® devices.
Additionally, the side effects haemorrhages and also intra- and subretinal fluids are identified in context of the state-of-the-art data. Haemorrhages, intra- and subretinal fluids are general complications that may occur when performing vitrectomy. In the state-of-the-art data and clinical data it is not described, that these side effects are directly related to the application of an endotamponade such as Densiron® 68 and Densiron® Xtra. Therefore, it is not necessary to include these side effects in the instructions for use.
Further, in the state-of-the-art data the side effect “migration of silicone oil” was described. However, the probability of occurrence of this side effect was so low (commuted to the total number of patients of all included studies) and not a single case was described in the clinical data, so that the inclusion of this side effect in the list of all Densiron® associated side effects is not necessary at the present time.

With the exception of eyes having a complex baseline situation, the indwelling time for Densiron® 68 / Densiron® Xtra should be kept as short as possible and limited to at most 3 months. A short length of indwelling time can reduce potential side effects and complications.

During removal of Densiron® 68 / Densiron® Xtra from the eye, attention must be paid to ensure that the heavy silicone oil tamponade is completely removed from the eye. Experience has shown that if the heavy silicone oil is removed in the post-operative phase, during which the visual acuity does not continue to increase or drops again, the final result of the surgery can be improved.

Densiron® 68 / Densiron® Xtra are not permitted to be used in patients that are hypersensitive to silicone oil and perfluorohexyloctane or wear a silicone intraocular lens (IOL). Because their density is greater than 1000 kg/m^3, Densiron® 68 / Densiron® Xtra are not permitted to be used in cases of superior retinal detachment. In addition, laser coagulation and cryotherapy are not permitted on eyes filled with Densiron® 68 / Densiron® Xtra.

Interactions with Densiron® 68 / Densiron® Xtra may occur if perfluorocarbons are not completely removed (e.g., sticky oil). There are currently no known interactions with other substances.

4.2. Warnings and precautions

- Do not use this device after the expiry date. The expiry date is shown on the devices and on the folding boxes.
- The device is only intended for single use on one patient. Repeated use may lead to microbial contamination, which may cause a severe infection in the patient.
- Use in pregnant women, nursing mothers and children is not recommended.
- Check the integrity of the sterile packaging. Do not use the device if the sterile packaging has been damaged.
- The indwelling time of the device should be kept as short as possible and limited to the recommended duration of use. A short length of indwelling time can reduce potential side effects and complications.
- A leak-free and safe connection of the syringe is ensured by the standardised Luer Lock (according to ISO 80369).
- Glass syringes are potentially fragile due to their material structure. It is recommended that appropriate application systems be used.
- Silicone oil could migrate out of the eye and could form lesions in the conjunctiva or eyelid.
- Avoid wetting the Luer-Lock thread of the syringe with the product Densiron® 68 / Densiron® Xtra. The wetting effect can potentially cause the Luer-Lock adapter to detach from the syringe.
- Before Densiron® 68 / Densiron® Xtra are permitted to be instilled in the eye, any heavy liquids, e.g., perfluorocarbons of any kind, must be completely removed from the vitreous chamber.
- Excessive instillation of Densiron® 68 / Densiron® Xtra in the posterior segment of the eye must be avoided.
- Densiron® 68 / Densiron® Xtra must be visually inspected for homogeneity and transparency prior to use. Products with phase separation or cloudiness must not be used.

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

During the current post-market surveillance period (2020 until July 2024) no kind of serious incident / adverse event / field safety corrective action (FSCA) concerning any Densiron® device did occur.

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

5.1. Summary of clinical data related to equivalent device

Not applicable, because the clinical evaluation and post-market clinical follow-up activity is based on published clinical data on the concerned devices Densiron® 68 and Densiron® Xtra itself.

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

Not applicable. No clinical investigation was necessary or performed for the product prior to CE marking.

5.3. Summary of clinical data from other sources

Clinical data obtained from scientific literature:

To gather the relevant publicly available information on the performance and safety of Densiron® 68 and Densiron® Xtra, a systematic literature search was performed in online databases. The search was conducted using keywords and operating of a search strategy. PubMed, NCBI and Scite_interfaces were searched as well as a search on a clinical trial portal was performed. The searches in clinical trial registries retrieved no relevant results.
Densiron® 68 / Densiron® Xtra have been on the market since 2003 / 2015 and these devices have been marketed all over the world for several years, respectively. Accordingly, an acceptable amount of publications on the clinical use of these medical devices are publicly available.
More than seventy publications on their clinical use were identified and were considered relevant and included for appraisal. All the publications stated Densiron® 68 / Densiron® Xtra as product tradename and most of them stated Fluoron GmbH or Geuder AG as manufacturer of the heavy silicone oils.

With regard to performance, procedural success (good tamponade effect, easy removal from the eye and low emulsification rate), anatomic success (re-attachment rate in cases of retinal detachment and macular hole closure rate for the treatment of macular holes) and functional success (improvement of visual acuity) have been identified as the parameters the concerned devices have to be compared to alternative treatments.

Procedural success
Good tamponade effect, easy removal from the eye and low emulsification rate
In the usability evaluation, the preparation and applicability of Densiron® 68 and Densiron® Xtra was rated by both distributors and medical personnel in a customer survey. Amongst others, the survey included questions on the quality of the tamponade effect and the removability of the endotamponade at the end of the indwelling time. On a scale from 1 to 5 (1=very good, 2=good, 3=intermediate, 4=poor, 5=very poor) the question on the tamponade effect was rated with 1.6 and 1.7 for Densiron® 68 and Densiron® Xtra, respectively. The ease of removal was rated with 1.7 and 2.1 for Densiron® 68 and Densiron® Xtra, respectively. Both criteria were within the specified acceptance criterion of ≤ 3 points.

The reattachment rate in cases of retinal detachment, closure rate of macular holes and the emulsification rate when using Densiron® 68 and Densiron® Xtra as long-term endotamponades are described in the literature: a primary reattachment rate of the retina of 83.57 % and final reattachment rate of 88.61 % in more than 1,800 patients, a primary macular hole closure rate of 84.35 % in more than 260 patients and a emulsification rate of 21.98 % in more than 760 patients reflect a successful tamponade of Densiron® 68 and Densiron® Xtra.

In addition, the tamponade effect of Densiron® 68 and Densiron® Xtra was described in the identified literature. A prospective, non-randomised, comparative, clinical pilot study was conducted (Abdelkader et al., 2011 [1]) to compare the effect of Densiron® 68 with silicone oil in 9 participants. The ‘separation volume’, defined as the relative volume of the space between intraocular tamponade agent and retina, was estimated using magnetic resonance imaging in both groups and the mean separation volume was statistically significantly larger in the silicone oil group (0.477±0.419 cm^3) than in the Densiron® 68 group (0.042±0.013 cm^3; P = 0.014). Thus Densiron® 68 achieved an excellent tamponade effect in the retina. Furthermore, the procedural success is connected to the anatomical success. Only if the retina is successfully reattached and/or retinal as well as macular holes are closed, a good tamponade effect can be achieved.

Anatomic success
Re-attachment rate in cases of retinal detachment
The anatomic success rates obtained with the concerned devices depend on the severity of the preoperative baseline situation. Good anatomic success rates leading to successful retinal reattachment in over 83 % of the cases have been reported with Densiron® 68 and Densiron® Xtra in various studies: Kocak and Koc, 2013 [2]; Romano et al., 2011 [3]; Herbrig et al., 2007 [4]; Caporossi et al., 2019b [5]; Levasseur et al., 2013 [6]; Kocak, 2014 [7]; Liu et al., 2014 [8]; Caporossi et al., 2019a [9]; Romano et al.,

2008 [10]; Felfeli et al., 2023 [11]; Tzoumas et al., 2024 [12]; Joussen et al., 2011 [13]; Li et al., 2010a [14]; Ozdek et al., 2011 [15]; Sanisoglu et al., 2014 [16]; Stappler et al., 2008 [17]; Alkawas et al., 2017 [18]; Sandner et al., 2007 [19]; Li et al., 2010b [20]; Sandner and Engelmann, 2006 [21]; Lim and Vote, 2008 [22]; Auriol et al., 2008 [23]; Wang et al., 2017 [24]; Mishra et al., 2021 [25]; Er, 2010 [26]; Wong et al., 2006 [27]; Zenoni et al., 2012 [28]; Wong et al., 2005 [29]; Stappler et al., 2009 [30]; Hussain and Banerjee, 2011 [31]; Schwarzer et al., 2014 [32]; Davidson et al., 2022 [33]; Aslankurt et al., 2012 [34] and Semeraro et al., 2019 [35]) accounting to as high as 100 % retinal reattachment in a few studies (Wong et al., 2009b [36]; Hostovsky et al., 2021 [37]; Hostovsky et al., 2020 [38]; Duan et al., 2011 [39]; Kurt and Kapran, 2022 [40]; Zewar et al., 2021b [41]; Szeligowski et al., 2024 [42]; Sobri et al., 2024 [43]; Keilani et al., 2019 [44]; MacGregor et al., 2017 [45]; Brunner et al., 2012 [46] and Roberts et al., 2024 [47]). Moreover, anatomical success in the form of attached retina has been achieved in 95.45 % cases of pediatric retinal detachment complicated proliferative vitreoretinopathy (PVR) (Mishra et al., 2021 [25]).
The most recent studies show that heavy silicone oil is an effective and reliable endotamponade in patients with (complicated) retinal redetachment and macular hole, in the presence of PVR, and in patients who require inferior retinal support (Kurt and Kapran, 2022 [40]; Felfeli et al., 2023 [11]). Densiron® 68 achieves higher anatomic success rates and improved visual outcomes compared with conventional light silicone oil in eyes with inferior retinal pathology and severe PVR (Tzoumas et al., 2024 [12]).

Macular hole closure rate for the treatment of macular holes
The concerned devices under assessment show comparable anatomical success rates as the results reported in meta-analyses and review articles as well as those observed with the similar device Oxane Hd. Thus, macular closure rates varied between 82 % and 100 % in the identified publications that reported this outcome parameter. In some of these studies, closure rates of Densiron® 68 tamponade were compared to silicone oil or gas tamponade, and results obtained with Densiron® 68 tamponade were equal to or better than with the other tamponade agents in all studies. For example, Cilino et al., 2016 [48] reported anatomical success was significantly higher in the Densiron® 68 group (82 %) than in the C_2F_6 group (30 %).
The results obtained with Densiron® 68 differ slightly from the predefined acceptance value (86 %) from state-of-the-art data. However, it should be noted that the macular closure rate for the devices under evaluation could be determined on the basis of 10 studies with more than 260 patients were included. For determining the acceptance value from state-of-the-art data only four publications with 51 patients were included. Furthermore, one study reported comparably low primary and secondary reattachment rates of 45.7 % and 50 %, respectively, after Densiron® 68 tamponade (Schaub et al., 2021 [49]). These low closure rates are probably due to the included severe conditions of persistent macular holes. Accordingly, results obtained with the comparator sulfur hexafluoride were in the same range (57.1 % and 50 %, respectively) as those obtained with Densiron® 68. As overall the determined macular hole closure rate of patients treated with Densiron® 68 is in the acceptance rate of using endotamponades for PPV, the efficacy of the product is given.

Functional success (improvement of visual acuity)
For the concerned device Densiron® 68, many patients experienced functional success with improved visual acuity in the range reported in meta-analyses and review articles for other tamponade agents. The vast majority of the 58 publications relevant to demonstrate performance of Densiron® 68 and Densiron® Xtra in severe retinal detachment, which included 2,160 patients altogether, reported best corrected visual acuity (BCVA) as functional outcome, which was expressed as logMAR, ETDRS letters, Snellen feet or decimal.

Retinal detachment
Altogether, 33 studies and 15 case reports/series including more than 1,800 patients reported clinical data on the visual acuity after treatment with Densiron® 68 and Densiron® Xtra. In most of the studies, stabilisation or improvement of the visual acuity was observed. Postoperative visual acuity was between count fingers and 1.96 logMAR in all studies.

Macular hole
Visual acuity was reported in ten studies using Densiron® 68 in macular hole surgery (Cillino et al., 2016 [48], Mete et al., 2011 [50], Szurman et al., 2021 [51], Avitabile et al., 2011 [52], Schaub et al., 2021 [49], Rizzo et al., 2009 [53], Lappas et al., 2009 [54], Schurmans et al., 2009 [55], Lohmann et al., 2022 [56] and Garcin et al., 2022 [57]).
These ten studies included four comparative studies. In three comparative studies, treatment with Densiron was compared to silicone oil (Mete et al., 2011 [50], Avitabile et al., 2011 [52]) or Sulfur hexafluoride (Schaub et al., 2021 [49]). In the further, fourth study by Szurman et al., 2021 [51] comparison included adjuvant intraoperative manipulation. In all four comparative studies, visual acuity improvement was comparable.

In summary, the reported BCVA for the concerned devices was comparable to alternative treatment options and tamponade agents for both treatment of severe retinal detachment and macular holes. As

overall the visual acuity of patients treated with Densiron has improved, the efficacy of the products in improving visual acuity has been proven.

Use of Densiron® in paediatric population
The efficacy and safety of Densiron® 68 as a primary endotamponade in the treatment of complex retinal detachment (RD) in children was evaluated in a prospective interventional case series involving 22 eyes in 22 children (less than 18 years of age, mean age 8.45 ± 3.36 years) (Mishra et al., 2021 [25]). Of these 22 children, 5 had total and subtotal retinal detachment each and 10 presented with inferior retinal detachment. All patient's had macula off RD at presentation. Standard three-port pars-plana vitrectomy without scleral buckling under general anaesthesia was surgical technique employed in all cases who were followed-up for 3 months. The anatomical success in the form of attached retinal was achieved in 21 (95.45 %) eyes. There was a significant association between duration of attachment of retina and PVR grade severity ($p < 0.05$).
Mishra et al., 2021 [25] concluded that Densiron can be an important endotamponade also in children. However, because this is supported by only limited amount of data, the use of Densiron® 68 and Densiron® Xtra in children is not recommended.

Use of Densiron® in pregnant women and nursing mothers
No studies have been identified that described the use of Densiron® 68 or of Densiron® Xtra in pregnant or breastfeeding women. As no clinical experience is available, use of Densiron® 68 or Densiron® Xtra is not recommended in pregnant women and nursing mothers.

Clinical safety data on Densiron®
In general, vitrectomy including the use of Densiron® 68 and Densiron® Xtra as long-term endotamponade is safe and effective and side effects / complications occur within an acceptable range. As for all surgical procedures, several complications have been observed with the use of Densiron® 68 and Densiron® Xtra. Clinical risks of the technology include anterior eye segment complications, decrease in visual acuity to vision loss, emulsification, decreased or increased intraocular pressure, retinal re-detachment, intraocular inflammations, new membrane formation and choroidal detachment.
One disadvantage for the patient is the fact that heavy silicone oil must be removed from the eye at the discretion of the treating physician by means of another procedure following stable re-attachment of the retina. However, this procedure can often be combined with a pending cataract operation in order to spare the patient from having to undergo an additional procedure.

With regard to safety, the PMS data analyses identified one new risk ("turbidity / cloudiness of the silicone oil during postoperative clinical follow-up"), which was evaluated as an acceptable risk. All other safety relevant data (device properties (e.g., durability, sterility), safety from in vitro tests, biocompatibility, non-clinical safety data, usability evaluation data, clinical data etc.) did not identify any special safety concern or risk in context of the use of Densiron® 68 / Densiron® Xtra.
The risk assessment of Densiron® was updated accordingly and resulted in the fact that the benefit still outweighs the possible risks in context of a Densiron® application. So, if the heavy silicone oils Densiron® are applied according to the intended use as specified in the instructions for use, a safe application of these tamponades can be guaranteed.

Included Literature in which the devices in question were used

[1] Abdelkader E, Siddiqui RM, Ramalingam S, Murrary A, Lois N. Heavier-than-water silicone oil mixture as a long-term tamponade agent: A pilot study. Ophthalmologica. 2011; 226 (SUPPL. 1): 60-65.

[2] Kocak I and Koc H. Comparison of Densiron 68 and 1000 cSt silicone oil in the management of rhegmatogenous retinal detachment with inferior breaks. Int J Ophthalmol 2013;6(1):81.

[3] Romano MR, Angi M, Valldeperas X, Costagliola C and Vinciguerra P. Twenty-three-gauge pars plana vitrectomy, Densiron 68, and 360 endolaser versus combined 20-gauge pars plana vitrectomy, scleral buckle, and SF6 for pseudophakic retinal detachment with inferior retinal breaks. Retina 2011; 31(4):686-691.

Included Literature in which the devices in question were used

[4] Herbrig E, Sandner D, Engelmann K. Anatomical and functional results of endotamponade with heavy silicone oil–Densiron® 68–in complicated retinal detachment. Ophthalmic Res 2007; 39(4): 198-206.

[5] Caporossi T, Tartaro R, Finocchio L, Barca F, Giansanti F, Franco F, Rizzo S. Perfluorodecalin versus Densiron® 68 heavy silicone oil in the management of inferior retinal detachment recurrence. Ophthalmic Surgery Lasers and Imaging Retina 2019b; 50(5): 274-280.

[6] Levasseur SD, Schendel S, Machuck RWA, Dhanda D. High-density silicone oil Densiron® 68 as an intraocular tamponade for primary inferior retinal detachments. Retina 2013; 33(3):627-633.

[7] Kocak I. Outcome of heavy silicone oil in the management of retinal detachment with inferior breaks. Inferior Yirtikli Retina Dekolmani Tedavisinde Agir Silikon Kullanilan Olgulardaki Sonuçlarimiz. Retina-Vitreus 2014; 22(3):209-212.

[8] Liu F, Li H, Feng L, Wang F. Anatomical and functional outcomes after Densiron® 68 heavy silicone oil tamponade for complicated retinal detachment in Chinese eyes. Int J Ophthalmol 2014;7(3):469-473.

[9] Caporossi T, Franco F, Finocchio L, et al. Densiron® 68 heavy silicone oil in the management of inferior retinal detachment recurrence: analysis on functional and anatomical outcomes and complications. Int J Ophthalmol 2019a; 12(4):615–620.

[10] Romano MR, Stappler T, Marticorena J, Groenewald C, Pearce I, Gibran S, Wong D, Heimann H. Primary vitrectomy with Densiron® 68 for rhegmatogenous retinal detachment. Graefe's Archive for Clinical and Experimental Ophthalmology 2008; 246(11):1541-1546.

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Clinical data obtained from Post Market Surveillance:

The following post-market surveillance activities were gathered and analysed: information concerning serious incidents, information from field safety corrective actions (FSCAs), data of complaints (involving non-serious incidents and undesirable side-effects), information on reporting trends, specialist literature data (state-of-the-art data and clinical data), technical literature data, data of regulatory and vigilance databases, data of similar devices, data of the post-market clinical follow-up (PMCF) activity and data of preventive and/or corrective actions (CAPA).

Information from serious incidents / field safety corrective actions

No kind of serious incident / adverse event or field safety corrective action (FSCA) concerning any Densiron® device did occur during the current post-market surveillance (PMS) period (from 2020 until July, 2024). So, data / information from serious incidents / adverse events / FSCAs concerning Densiron® devices do not exist.

Complaints

During the complaint data collection period (2020 until 30th July 2024) the annual Densiron® complaint rate was relatively low (≤ 0.02 %), respectively. Further, in total five complaints in association with Densiron® application were reported to Fluoron GmbH.

All types of complaints occurred only once in the period 2020 until 30th July 2024 and all these risks have already been evaluated within the risk analysis of the Densiron® devices.

Further, the real probabilities of occurrence of all reported Densiron® complaints were calculated. Resulting from this calculation, the previously estimated values for the probability of occurrence of three Densiron®

risks were adjusted, however these risks remained within the acceptable range.

Trend reporting
The feedback from the market did not result in any changes in the assessment of severity of harm.
However, the Densiron® PMS data analysis of the complaint data resulted in changes of the probabilities of occurrence of three risks, but all these risks are evaluated as acceptable risks.
Thus, the medical benefit of the medical devices Densiron® still outweighs the possible risks of using these heavy silicone oils. That means, a reportable trend according to the Article 88 of the MDR 2017/745 does not exist.

Post-market clinical follow-up (PMCF) activity / Specialist literature data
As a PMCF activity, a literature search was performed. This literature search review resulted in publications describing the medical devices Densiron® 68 and Densiron® Xtra or similar devices during use on treatment of retinal detachment or on macular hole treatment. These state-of-the-art and clinical literature data have an appropriate quality to represent relatively good the actual clinical performance and safety of the medical devices Densiron® 68 and Densiron® Xtra, respectively. Further, in context of this literature search no new risk / side effect in association with using a heavy silicone oil tamponade was identified. Thus, the acceptance of the benefit-risk ratio of the Densiron® 68 / Densiron® Xtra medical devices is continued guaranteed. Furthermore, the literature data showed that the known side effects occurred in association with Densiron® 68 / Densiron® Xtra application are well within the normal range of patients suffering from a complicated retinal detachment or a macular hole.

Technical literature data
The review of the technical literature data – relevant applicable standards / laws / regulations / guidelines – showed, that the Densiron® devices are manufactured in conformity with current standards/guidelines and legislation.

Data of regulatory and vigilance databases
Searches in regulatory/vigilance databases of different countries:
The searches in the MAUDE database (database of the U.S. Food & Drug Administration) and the database of Health Canada with the chosen keywords “Densiron” and “heavy AND silicone oil AND intraocular” resulted in some hits, respectively.
All five hits resulted from the MAUDE database are not relevant for the medical devices Densiron®.
Further, in total 26 hits resulted from the database of Health Canada, 23 hits are not relevant and 3 hits are relevant for Densiron®.
These three relevant hits do not reflect any new identified potential hazard / risk, which have to be included in the risk analysis of the medical devices Densiron®.

Detailed search in BfArM’s database (database of the German Federal Institute for Drugs and Medical Devices):
The detailed search of the BfArM’s database aimed 81 relevant hits and 112 non-relevant hits. This search revealed that the risk “turbidity / cloudiness of the silicone oil during postoperative clinical follow-up”, which was identified in context of the voluntary recall of some Siluron® batches of Fluoron GmbH in October 2023 (BfArM reference number: 30253/23), is also valid for the Densiron® devices. So, this risk was added to the risk assessment of the Densiron® device group.

Data of similar medical devices
The publicly available information gathered of the one medical device, which is presumed to be similar to the Densiron® devices, show the following result:
All the clinical / biological / technical characteristics of the Densiron® devices and the one competitor device Oxane Hd are similar or equivalent. That means this competitor device Oxane Hd is a similar device to the medical devices Densiron® concerning the clinical / biological / technical characteristics, respectively.

Preventive and/or corrective actions (CAPA)
All CAPAs of internal non-conformities and such CAPAs resulting from audits (external, internal) were assessed for any direct impact on product safety, performance or quality. The result of this CAPA evaluation for current post-market surveillance time period from 2019 until June, 2024 showed that no CAPAs were detected, which had a direct impact on product safety, performance or quality of the medical devices Densiron® 68 and Densiron® Xtra.

Overall summary clinical data obtained from Post Market Surveillance
From the Densiron® post-market surveillance (PMS) activities one new risk was identified.
No new benefits of the medical devices Densiron® were identified during the post-market surveillance of these devices.

Furthermore, the PMS data analyses of the Densiron® 68/Xtra devices do not result in any changes in the assessment of severity of harm.
Further, the PMS data analyses of the Densiron® devices result in changes in the assessment of probability of occurrence of three risks. However, all these three risks remain acceptable risks in context of the risk assessment of the Densiron® device group, respectively.

So, the following is valid for the Densiron® devices:
Based on the analyses of the collected PMS data, it is concluded that the benefit-risk profile of the medical devices Densiron® 68/Xtra has not been adversely impacted, i.e. remains unchanged.

Clinical data from medical device registries:
Not applicable. Registries are not performed with the medical devices under assessment.

5.4. An overall summary of the clinical performance and safety

Performance:
With regard to performance, the following parameters are considered as relevant for the Densiron® devices:
good tamponade effect, easy removal from the eye and low emulsification rate (procedural success), re-attachment rate in cases of retinal detachment and macular hole closure rate for the treatment of macular holes (anatomic success) and improvement of visual acuity (functional success).
Overall, the procedural, anatomical and functional success rates are comparable with values reported for comparable long-term tamponades and benchmark devices in the state of the art. That means Densiron® 68 / Densiron® Xtra can be used successfully as long-term tamponade for the treatment of retinal detachment and as tamponades in macular hole surgery. Performance of these heavy silicone oil tamponades is adequately supported with clinical data for the claimed indications and patient populations and can therefore be regarded as proven.

Safety:
With regard to safety, the safety relevant data such as device properties (e.g., chemically and physiologically inert, non-toxic, biocompatible, ultrapure), safety from in vitro tests, non-clinical safety data, usability evaluation data, post-market surveillance data, clinical data etc. did not identify any special safety concern or risk in context of the use of Densiron® 68 / Densiron® Xtra.
Further, the following risks have been reported for Densiron® 68 / Densiron® Xtra in the identified publications on clinical data or become apparent from PMS activities or through searches in regulatory and vigilance databases: anterior eye segment complications, decrease in visual acuity to vision loss, emulsification, decreased or increased intraocular pressure, retinal re-detachment, intraocular inflammations, new membrane formation and choroidal detachment.
These risks (side effects / complications) described in context of application of a Densiron® device are well within the normal range of patients suffering from complicated retinal detachment or a macular hole as compared to the similar devices.
Further, the detailed research of the German vigilance database (BfArM) performed as a PMS activity identified one new risk (“turbidity / cloudiness of the silicone oil during postoperative clinical follow-up”), which was evaluated within the Densiron® risk assessment, and corresponding risk control measures were implemented. The risk evaluation showed that the benefit still outweighs the possible risks in context of a Densiron® 68 / Xtra application.

Conclusion
The clinical performance and safety of the heavy silicone oil tamponades Densiron® 68 / Xtra have been verified based on clinical literature data, the usability evaluation data and the post-market surveillance data.
So, if the Densiron® devices are applied according to the intended use as specified in the instructions for use, there is no concern on the acceptability of the well-known undesirable side effects, and the benefit outweighs the possible risks in context of a Densiron® 68 / Xtra application.

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

PMCF activity: Systematic literature review

A systematic literature search was performed to gather and evaluate state-of-the-art data and clinical data on the medical devices Densiron® 68 and Densiron® Xtra for confirmation the clinical evidence (safety and clinical performance) of these medical devices.

Description of activity	Aim of the activity	Rationale and known limitations of the activity	Timelines of the activity
Systematic literature review	**Continuous evaluation of the evidence (safety and performance) from Densiron® 68/Xtra and defined similar products**	**Systematic literature search review (including literature search plan, literature search protocol and literature search report) according to the requirements of MEDDEV 2.7.1 Rev. 4 and the MDR 2017/745.** **The systematic literature search (state of the art and clinical data) will be organized and performed in a structured and preplanned way. A well-constructed search strategy will be prepared using keywords. The search strategy will be documented in a literature search plan. To allow the reproduction of the systematic searches, the following information will be documented in a literature search protocol: databases searched, dates of the searches, search queries (incl. search terms and restrictions), covered time period and results. The results of the literature search will be documented in a literature search report.**	**Literature review will be finalized until Q3 2024**

Unanswered questions relating to the use of the devices:
There are no unanswered questions relating to the use of the Densiron® devices; therefore, further investigations are not applicable.

Detection of emerging risks, complications or unexpected device failures:
In the context of the performed PMCF activity systematic literature review, no new risk or any new side effect of the Densiron® devices was identified. So, the medical benefit of the device group Densiron® still outweighs the possible risks of using the Densiron® devices, respectively.

6. Possible diagnostic or therapeutic alternatives

The vitreous body is a gelatinous substance mainly composed of water, with structural components of hyaluronic acid and different types of collagen. It fills the vitreous chamber, the space between the lens and the retina. Due to its viscoelastic properties it absorbs the stress and strain of the bulb during the movement. Besides its role as a filling substance, the vitreous also has an active role in ocular physiology. The presence of active cells and molecules allows control over inflammation, proliferation, and neovascularisation. In addition, it acts as a barrier to bacterial infection and as repository for oxygen and nutrients. Since 1960, researchers have tried to find adequate substitutes to replace the physical and biological functions of the vitreous. Different currently available tamponade agents able to fulfil this function are summarised below.

Gas
Small volumes of undiluted gas are typically used for pneumatic retinopexy, larger volumes for pars plana vitrectomy. Sulphur hexafluoride (SF_6), perfluoroethane (C_2F_6) and perfluoropropane (C_3F_8) are the most commonly used gases. They present a high surface tension and a specific gravity lower than water to maintain the tamponade effect. SF_6 exerts an effect for 1 to 2 weeks, whereas C_3F_8 persists for 6 to 8 weeks. Due to their longer permanence compared to air they represent the standard gases used in pneumatic retinopexy and vitreoretinal surgery. As with air, the buoyancy (upward force) of the gas bubble keeps the retina against the pigment epithelium. Due to their very low specific gravities (0.001 g/ml) they have a much greater buoyancy than silicone oils. Because the effect is greatest at the upper side of the bubble, this results in a good tamponade of the upper retina, while the patient is in an upright position, but a less effective support of the lower retina. Fundus evaluation is problematic until gas reabsorption due to the lower refractive index of the gases, which causes almost complete reflection of light. Patients with intraocular gases should be advised against air travel or traveling to high altitude, and they should avoid diving. The advantage of these gases is that they are slowly removed via the blood and replaced with aqueous humour. This makes it unnecessary to perform another surgical procedure to remove the gas from the eye, as in the case of the silicone oils. Due to the fact that gases expand rapidly with any drop in air pressure, travel by plane, stay at higher elevations and diving are contraindicated in cases where the vitreous cavity has been instilled with gas.

Silicone oils
Silicone oils have been used to act as internal tamponades in vitreoretinal surgery procedures for more than 40 years. Their use as intra-operative tool to stabilise the retina can be adopted in difficult cases of retinal detachment such as those complicated with proliferative vitreoretinopathy, giant retinal tears, and penetrating ocular trauma. With the introduction of pars plana vitrectomy, silicone oils became also the standard medium for post-operative long-term tamponade in the vitreous cavity following re-attachment of the retina. Silicone oil agents are used to ensure retinal adherence following retinopexy for the time necessary to generate a permanent seal, to control intraocular haemorrhages, and to maintain intraocular pressure. As with gas, the good tamponade effect of silicone oils is restricted to the upper retina when the patients head is in an upright position. Lately developed silicone oil blends contain 5-10% long chain high molecular weight silicone oil (2.5 Mio mPas, 423 kDa) and 90-95% 1000 mPas silicone oil. By adding 5-10% high molecular weight silicone oil the shear viscosity increases, providing the oils with a high resistance to emulsification and maintaining good injectability.

Heavy silicone oils
Heavy silicone oils are homogenous solutions of two substances used as a single tamponade agent with improved properties. That means the advantageous characteristics of both substances (silicone oil and perfluorohexyloctane (F6H8)) are combined within the heavy silicone oils: silicone oil with higher viscosity, lower emulsification, higher surface tension against water, more stable bubble and lower dispersion along with the higher specific density and better contact of F6H8.
The common products belonging to the heavy silicone oil group that are available for clinical use: Densiron® 68 and Densiron® Xtra both manufactured by Fluoron GmbH (a combination of F6H8® and silicone oil) and Oxane® HD (Bausch and Lomb: a combination of olefin RMN3 and silicone oil), which are well tolerated and efficiently used. Oxane® HD, Densiron® 68 and Densiron® Xtra, all contain a silicone oil and a semifluorinated alkane component, but in different ratios resulting in different specific gravities and viscosities.

Like silicone oils, heavy silicone oils have good transparency and are chemically inert. Standard gas or silicone oil endotamponades are unable to provide satisfactory retinal support in the usual upright and supine positions. Heavier-than-water intraocular tamponades are easier to apply and due to their high specific gravity offer the potential to provide adequate support, not requiring an uncomfortable prone position for postoperative maintenance. Due to their higher than water density, they are useful tamponade agents in all cases where an effect on the inferior parts of the retina is required, thus stabilizing the lower retinal layer, and sealing the cracks. Heavy silicone oils thus provide benefit in complicated situations such as Rhegmatogenous retinal detachment, associated with large breaks in lower periphery being supported in upright position, interruption of retinal pigment epithelial cells and peri-retinal space, displacement of proliferative mixture of aqueous inflammatory and retinal pigment epithelium cells away from lower retina and faster and lasting macular reattachments.

7. Suggested profile and training for users

Densiron® 68 / Densiron® Xtra devices are prepared and used exclusively by qualified personnel for intraocular surgery. They have completed a medical degree and the corresponding specialist training. The users have experience with comparable products, because silicone oil tamponades and heavy silicone oil tamponades belong to the usual aids in the field of ophthalmic surgery.
Patients themselves have no opportunity to apply and/or influence the medical device.

8. Reference to any harmonised standards and CS applied

Directives and laws:

COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices (Medical Device Directive)

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Directives 90/385/EEC and 93/42/EEC (last consolidated version).

COMMISSION RECOMMENDATION of 24 September 2013 on the audits and assessments performed by notified bodies in the field of medical devices ((EU) 2013/473)

Implementing rules for Regulation (EU) 2017/745 of the European Parliament and of the Council as regards electronic instructions for use for medical devices ((EU) 2021/2226)

Commission Implementing Regulation (EU) 2021/2078 of 26 November 2021 laying down detailed rules for the implementation of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards the European database for medical devices (Eudamed)

Regulation (EU) 2023/607 of the European Parliament and of the Council of 15 March 2023 amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards transitional provisions for certain medical devices and in vitro diagnostic medical devices

Commission Implementing Decision (EU) 2021/1182 of 16 July 2021 on harmonised standards for medical devices in supporting Regulation (EU) 2017/745 of the European Parliament and of the Council (last consolidated version)

Regulation (EU) 2024/1860 of the European Parliament and of the Council of 13 June 2024 amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards the phasing-in of Eudamed, the obligation to provide information in the event of interruption or cessation of supply and the transitional provisions for certain in vitro diagnostic medical devices

Ordinance Regulating the Dispensing of Medical Devices (Medical Devices Dispensing Ordinance – MPAV))

Medical Devices Implementation Act (MPDG)

Medical Devices User Notification and Information Ordinance (MPAMIV)

Medical Device Adaptation Act EU (MPAnpG-Eu)

Medical Devices Operator Ordinance (MPBetreibV)

Therapeutic Products Advertising Act (HWG)

Guidances:

MEDDEV 2.7/1, Rev. 4: 2016-06: Clinical evaluation: A guide for manufacturers and notified bodies

MEDDEV 2.12-1, Rev. 8: 2013-01: Guidelines on a medical devices vigilance system

GHTF (Study Group 3): 2004-02: Quality Management Systems – Process Validation Guidance

European Pharmacopeia (Ph. Eur.), edition 11: 2023-01

MDCG 2019-9, Rev.1: 2022-03: Summary of safety and clinical performance

MDCG 2019-8 v2: 2020-03: Guidance document implant card on the application of Article 18 Regulation (EU) 2017/745 on medical devices

MDCG 2020-7: 2020-04: Guidance on PMCF plan template

MDCG 2020-8: 2020-04: Guidance on PMCF evaluation report template

MDCG 2020-3, Rev.1: 2023-05: Guidance on significant changes regarding the transitional provision under Article 120 of the MDR with regard to devices covered by certificates according to MDD or AIMDD

MDCG 2020-6: 2020-04: Guidance on Sufficient Clinical Evidence for Legacy Devices: Background note on the relationship between MDCG 2020-6 and MEDDEV 2.7/1 rev.4 on clinical evaluation

MDCG 2020-5: 2020-04: Guidance on Clinical Evaluation - Equivalence

MDCG 2020-13: 2020-07: Clinical evaluation assessment report template

MDCG 2018-1, Rev.4: 2021-04: Guidance on BASIC UDI-DI and changes to UDI-DI

MDCG 2021-19: 2021-07: Guidance note integration of the UDI within an organisation’s quality management system

MDCG 2021-25, Rev.1: 2024-10: Application of MDR requirements to “legacy devices” and to devices placed on the market prior to 26 May 2021 in accordance with Directives 90/385/EEC or 93/42/EEC

MDCG 2019-14: 2019-12: Explanatory note on MDR codes

EMDN V1.1: 2021-09: European Medical Device Nomenclature (EMDN)

CND: 2020-01: The CND nomenclature – Background and general principles

NBOG_BPG_2009-3: 2009-03: Guideline for Designating Authorities to Define the Notification Scope of a Notified Body Conducting Medical Devices Assessments

MDCG 2021-24: 2021-10: Guidance on classification of medical devices

MDCG 2022-4, Rev.2: 2024-05: Guidance on appropriate surveillance regarding the transitional provisions under Article 120 of the MDR with regard to devices covered by certificates according to the MDD or the AIMDD

MDCG 2022-21: 2022-12: Guidance on Periodic Safety Update Report (PSUR) according to Regulation (EU) 2017/745

MDCG 2023-3, Rev.1: 2024-11: Questions and Answers on vigilance terms and concepts as outlined in the Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746

Standards:

DIN EN ISO 13485: 2021-12: Medical devices - Quality management systems - Requirements for regulatory purposes (ISO 13485:2016); German version EN ISO 13485:2016 + AC:2018 + A11:2021

DIN EN ISO 14971: 2022-04: Medical devices - Application of risk management to Medical devices (ISO 14971:2019); German version EN ISO 14971:2019 + A11:2021

ISO/TR 24971: 2020-06: Medical devices - Guidance for the use of ISO 14971

DIN EN ISO 15223-1: 2022-02: Medical devices - Symbols for use in the information supplied by the manufacturer - Part 1: General requirements (ISO 15223-1:2021); German version EN ISO 15223-1:2021

DIN EN ISO 20417: 2022-03: Medical devices - Requirements for information to be provided by the manufacturer (ISO 20417:2021, corrected version 2021-12); German version EN ISO 20417:2021

DIN EN 62366-1: 2021-08: Medical devices - Part 1: Application of fitness for use to medical devices (IEC 62366-1:2015 + COR1:2016 + A1:2020); German version EN 62366-1:2015 + AC:2015 + A1:2020

DIN EN ISO 14155: 2021-05: Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155:2020); German version EN ISO 14155:2020

DIN EN ISO 11737-1: 2021-10: Sterilisation of health care products – Microbiological methods - Part 1: Determination of the population of microorganisms on products (ISO 11737-1: 2018 + Amd 1: 2021); German version EN ISO 11737-1: 2018 + A1: 2021)

DIN EN ISO 11737-2: 2020-07: Sterilisation of health care products – Microbiological methods – Part 2: Sterility testing in the definition, validation and maintenance of a sterilization process. (ISO 11737-1: 2019); German version EN ISO 11737-2: 2020

DIN EN ISO 10993-1: 2021-05: Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management system (ISO 10993-1:2018, including corrected version 2018-10); German version EN ISO 10993-1:2020.

DIN EN ISO 10993-2: 2023-02: Biological evaluation of medical devices - Part 2: Animal welfare requirements (ISO 10993-2:2022); German version EN ISO 10993-2:2022

DIN EN ISO 10993-3: 2015-02: Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity (ISO 10993-3:2014); German version EN ISO 10993-3:2014.

DIN EN ISO 10993-5: 2009-10: Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity (ISO 10993-5:2009); German version EN ISO 10993-5:2009

DIN EN ISO 10993-6: 2017-09: Biological evaluation of medical devices - Part 6: Tests for local effects after implantation (ISO 10993-6:2016); German version EN ISO 10993-6:2016.

DIN EN ISO 10993-9: 2022-03: Biological evaluation of medical devices - Part 9: Framework for the identification and quantification of potential degradation products (ISO 10993-9:2019); German version EN ISO 10993-9:2021

DIN EN ISO 10993-10: 2023-04: Biological evaluation of medical devices - Part 10: Tests for skin sensitization (ISO 10993-10:2021); German version EN ISO 10993-10:2023

DIN EN ISO 10993-11: 2018-09: Biological evaluation of medical devices - Part 11: Tests for systemic toxicity (ISO 10993-11:2017); German version EN ISO 10993-11:2018.

DIN EN ISO 10993-12: 2021-08: Biological evaluation of medical devices - Part 12: Sample preparation and reference materials (ISO 10993-12:2021); German version EN ISO 10993-12:2021

DIN EN ISO 10993-17: 2024-02: Biological evaluation of medical devices – Part 17: Toxicological risk assessment of medical device components (ISO 10993-17:2023); German version EN ISO 10993-17:2023

DIN EN ISO 10993-18: 2023-11: Biological evaluation of medical devices – Part 18: Chemical characterization of materials for medical devices in the context of a risk management system (ISO 10993-18:2020 + Amd 1:2022); German version EN ISO 10993-18:2020 + A1:2023

DIN EN 556-1: 2024-09: Sterilization of medical devices – Requirements for medical devices labelled ‘STERILE’ – Part 1: Requirements for medical devices sterilized in the final pack; German version EN 556-1:2024

DIN EN ISO 17665: 2024-09: Sterilisation of health care products – Moist heat – Requirements for the development, validation and control of the use of a sterilization process for medical devices (ISO 17665:2024); German version EN ISO 17665:2024

DIN EN ISO 20857: 2013-08: Sterilisation of health care products - Dry Heat - Requirements for the

development, validation and control of the of the application of a sterilization process for medical devices (ISO 20857:2010); German version EN ISO 20857:2013

DIN EN ISO 11607-1: 2024-02: Packaging for medical devices to be sterilized in the final packaging – Part 1: Requirements for materials, sterile barrier systems and packaging systems (ISO 11607-1:2019 + Amd 1:2023); German version EN ISO 11607-1:2020 + A1:2023

DIN EN ISO 11607-2: 2024-02: Packaging for medical devices to be sterilized in the final packaging – Part 2: Validation requirements for processes of moulding, sealing and assembling (ISO 11607-2:2019 + Amd 1:2023); German version EN ISO 11607-2:2020 + A1: 2023

DIN EN 868-2: 2017-05: Packaging for terminally sterilized medical devices - Part 2: Sterilization packaging - Requirements and test methods; German version EN 868-2:2009

DIN EN 868-5: 2019-03: Packaging for terminally sterilized medical devices - Part 5: Sealable transparent pouches and tubes made of porous materials and plastic laminated film - Requirements and test methods; German version EN 868-5:2018

DIN EN 17141: 2021-02: Cleanrooms and associated cleanroom areas - Biocontamination control; German version EN 17141:2020

DIN EN ISO 14644-1: 2016-06: Cleanrooms and associated cleanroom environments - Part 1: Classification of air cleanliness based on particle concentration (ISO 14644-1:2015); German version EN ISO 14644-1:2015

DIN EN ISO 14644-2: 2016-05: Cleanrooms and associated cleanroom areas - Part 2: Monitoring to demonstrate cleanroom performance with respect to air purity using particle concentration (ISO 14644-2:2015); German version EN ISO 14644-2:2015

DIN EN ISO 14644-3: 2020-08: Cleanrooms and associated cleanroom areas - Part 3: Test methods (ISO 14644-3:2019, corrected version 2020-06); German version EN ISO 14644-3:2019.

DIN EN ISO 14644-4: 2023-04: Cleanrooms and associated cleanroom areas - Part 4: Planning, design, construction and initial commissioning (ISO 14644-4:2022); German version EN ISO 14644-4:2022

DIN EN ISO 14644-5: 2005-03: Cleanrooms and associated cleanroom areas - Part 5: Operation (ISO 14644-5:2004); German version EN ISO 14644-5:2004

DIN EN ISO 14644-7: 2005-01: Cleanrooms and associated cleanroom environments - Part 7: SD modules (clean air bonnets, glove boxes, isolators and minienvironments) (ISO 14644-7:2004); German version EN ISO 14644-7:2004

DIN EN ISO 14644-8: 2022-10: Cleanrooms and associated cleanroom areas - Part 8: Chemical air cleanliness assessment (ACC) (ISO 14644-8:2022); German version version EN ISO 14644-8:2022

DIN EN ISO 14644-9: 2022-10: Cleanrooms and associated cleanroom areas - Part 9: Evaluation of of particulate surface cleanliness (ISO 14644-9:2022); German version version EN ISO 14644-9:2022

DIN EN ISO 14644-10: 2022-10: Cleanrooms and associated cleanroom areas - Part 10: Assessment of chemical surface cleanliness (ISO 14644-10:2022); German version EN ISO 14644-10:2022

DIN EN ISO 14644-13: 2017-11: Cleanrooms and associated cleanroom areas - Part 13: Cleaning of surfaces to achieve defined cleanliness levels with respect to particle and chemical classifications (ISO 14644-13:2017); German version EN ISO 14644-13:2017.

DIN EN ISO 14644-14: 2017-01: Cleanrooms and associated cleanroom environments - Part 14: Evaluation of cleanroom suitability of equipment by airborne particle concentration (ISO 14644-14:2016); German version EN ISO 14644-14:2016.

DIN EN ISO 14644-15: 2018-03: Cleanrooms and associated cleanroom environments - Part 15: Assessment of cleanroom suitability of equipment and materials using air and surface chemical concentrations (ISO 14644-15:2017); German version EN ISO 14644-15:2017.

DIN EN ISO 14630: 2013-03: Non-active surgical implants - General requirements (ISO 14630:2012); German version EN ISO 14630:2012

DIN EN ISO 14937: 2010-03: Sterilization of health care products - General requirements for the characterization of a sterilizing agent and for the development, validation and control of the use of a

sterilization process for medical devices (ISO 14937:2009); German version EN ISO 14937:2009

DIN EN ISO 16672: 2022-05: Ophthalmic implants - Ocular endotamponades (ISO 16672:2020); German version EN ISO 16672:2021

DIN EN ISO 3166-1: 2020-12: Codes for the names of countries and their subdivisions - Part 1: Codes for country names (ISO 3166-1:2020); English version EN ISO 3166-1:2020

DIN ISO 10002: 2019-07: Quality management - Customer satisfaction - Guidance for complaint handling in organizations (ISO 10002:2018)

DIN EN ISO 11138-4: 2017-07: Sterilization of health care products - Biological indicators - Part 4: Biological indicators for dry heat sterilization processes (ISO 11138-4:2017); German version EN ISO 11138-4:2017

DIN EN ISO 11138-3: 2017-07: Sterilization of health care products - Biological indicators - Part 3: Biological indicators for moist heat sterilization processes (ISO 11138-3:2017); German version EN ISO 11138-3:2017.

DIN EN ISO 80369-7: 2021-08: Small diameter connectors for liquids and gases in medical applications – Part 7: Connectors for intravascular or hypodermic applications (ISO 80369-7: 2021); German version EN ISO 80369-7: 2021

DIN EN 285: 2021-12: Sterilisation – Steam sterilisers – Large sterilisers; German version EN 285:2015+A1:2021

ASTM D4169-23e1: 2024-03: Standard Practice for Performance Testing of Shipping Containers and Systems

ASTM D4332-22: 2022-06: Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing

ASTM D5276-19(2023): 2023-10: Standard Test Method for Drop Test of Loaded Containers by Free Fall

ASTM D642-20: 2020-10: Standard Test Method for Determining Compressive Resistance of Shipping Containers, Components, and Unit Loads

ASTM D4728-17(2022): 2022-05: Standard Test Method for Random Vibration Testing of Shipping Containers

ASTM D6344-04 (2024): 2024-10: Standard Test Method for Concentrated Impacts to Transport Packages

ASTM F-1886/F1886M (2024): 2024-11: Standard Test Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection

ASTM F3039-23: 2023-06: Standard Test Method for Detecting Leaks in Nonporous Packaging or Flexible Barrier Materials by Dye Penetration

ASTM F88/F88M-23: 2023-08: Standard Test Method for Seal Strength of Flexible Barrier Materials

ASTM F1929-23: 2023-12: Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration

ASTM D6499-24: 2024-06: Standard Test Method for Immunological Measurement of Antigenic Protein in Hevea Natural Rubber (HNR) and its Products

ASTM F1980-21: 2021-12: Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices

A summary of the safety and clinical performance of the device, intended for patients, is given below.

Summary of safety and clinical performance

Document revision: 07

Date issued: 02/2025

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 information presented below is intended for patients or lay persons. A more extensive summary of its safety and clinical performance prepared for healthcare professionals is found in the first part of this document.

The SSCP is not intended to give general advice on the treatment of a medical condition. Please contact your healthcare professional in case you have questions about your medical condition or about the use of the device in your situation. This SSCP is not intended to replace an Implant card or the Instructions For Use to provide information on the safe use of the device.

1. Device identification and general information

o Device trade name

Densiron® 68 / Densiron® Xtra

o Manufacturer; name and address

Fluoron® GmbH
Gesellschaft für hochreine Biomaterialien
Magirus-Deutz-Straße 10
89077 Ulm
Germany

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Email: info@fluoron.de
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o Basic UDI-DI

4260160455035K

o Year when the device was first CE-marked

Product	Year
Densiron® 68	2003
Densiron® Xtra	2015

2. Intended use of the device

o Intended purpose

Densiron® 68/Densiron® Xtra are sterile medical devices composed of a mixture of ultrapure silicone oil (polydimethylsiloxane) and an ultrapure, semifluorinated alkane (perfluorohexyloctane). Densiron® 68/Densiron® Xtra are used as postoperative long-term endotamponades in the field of ophthalmic surgery.

o Indications and intended patient groups

Densiron® 68/Densiron® Xtra are intended only for ocular application. Densiron® 68/ Densiron® Xtra are used for the treatment of severe cases of retinal detachment, especially for:

- Inferior and posterior retinal holes
- Retinal detachments with giant tears
- Retinal detachments with proliferative vitreoretinopathy (PVR)
- Traumatic retinal detachments.

Densiron® 68 and Densiron® Xtra are also used as a tamponade in macular hole surgery.

Intended patient population: Patients requiring surgical treatment of severe retinal detachment or surgical treatment of a macular hole. Use in pregnant women, nursing mothers, and children is not recommended.

o Contraindications

Densiron® 68 / Densiron® Xtra are not permitted to be used in patients that are hypersensitive to silicone oil and perfluorohexyloctane or wear a silicone intraocular lens (IOL). Because their density is greater than 1000 kg/m^3, Densiron® 68 / Densiron® Xtra are not permitted to be used in cases of superior retinal detachment. In addition, laser coagulation and cryotherapy are not permitted on eyes filled with Densiron® 68 / Densiron® Xtra.

3. Device description

o Device description and material/substances in contact with patient tissues

Densiron® 68 and Densiron® Xtra are sterile, colourless, homogenous liquids composed of a mixture of ultrapure polydimethylsiloxane (silicone oil) and ultrapure perfluorohexyloctane (semifluorinated alkane). Both, silicone oils and semifluorinated alkanes, are commonly used in retinal surgery.

Densiron® 68 and Densiron® Xtra are well-established devices and are used as a long-term tamponade for the treatment of severe cases of retinal detachment, especially for inferior and posterior retinal holes, retinal detachments with giant tears, retinal detachments with proliferative vitreoretinopathy (PVR) and traumatic retinal detachments. Densiron® 68 and Densiron® Xtra are also used as a tamponade in macular hole surgery.

Densiron® 68 and Densiron® Xtra differ only with regard to the silicone oil: Densiron® 68 contains Siluron® 5000 with dynamic viscosity of 4600 - 5600 mPas (at 25 °C ± 2 °C) and Densiron® Xtra contains Siluron® Xtra with dynamic viscosity of 4100-5000 mPas (at 25 °C ± 2 °C, both Fluoron GmbH). The lower viscosity of Densiron® Xtra leads to shorter injection times compared with Densiron® 68, and emulsification rates are also lower.

o Information about medicinal substances in the device, if any

Densiron® 68 / Densiron® Xtra contain no biologically active components, are chemically and physiologically inert and non-toxic. The medical devices are not radioactive, have no pharmacological effect, and contain no medicinal products or tissue or blood products of animal or human origin.

o Description of how the device is achieving its intended mode of action

Densiron® 68 / Densiron® Xtra are used as long-term tamponades for treatment of severe cases of retinal detachment as well as in macular hole surgery.
With the exception of eyes having a complex baseline situation, the indwelling time for Densiron® 68 / Densiron® Xtra should be kept as short as possible and limited to at most 3 months.

o Description of accessories, if any

No specific accessories are necessary for the application of Densiron® 68 / Densiron® Xtra according to intended use.

4. Risks and warnings

Contact your healthcare professional if you believe that you are experiencing side effects related to the device or its use or if you are concerned about risks. This document is not intended to replace a consultation with your healthcare professional if needed.

o How potential risks have been controlled or managed

If you, as a patient, believe that you are experiencing an adverse reaction related to the product or its use, so please contact Fluoron GmbH immediately via e-mail *complaints@fluoron.de* or the competent authority of your country.

On the basis of the continuous surveillance of the medical devices on the market (post-market surveillance), potential risks that may arise in connection with the use of the Fluoron device are reviewed. Furthermore, existing risks are reduced by implementing appropriate risk control measures to acceptable residual risks, if possible.

o Remaining risks and undesirable effects

Side effects / complications associated with vitrectomy together with the application of Densiron® 68 / Densiron® Xtra and identified via clinical literature data (resulted from a systematic review of scientific literature) and via complaints reported the Fluoron GmbH in context of Densiron® device application are described in the following:

Side effects and complications	**Expected frequency**	**Time of occurrence (intraoperative, postoperative)**
Anterior eye segment complications (e.g. cataract *(clouding or loss of transparency of the lens in the eye)*, corneal complications (*disorders of the outermost layer of the eyeball in the area in front of the lens))*	> 1 of 1000	postoperative
Decrease in visual acuity to vision loss *(e.g. blurred vision)*	> 1 of 1000000 and ≤ 1 of 100000	postoperative
Emulsification *(Separation of small stable droplets from a large silicone oil bubble; happens continuously at the (phase) boundary between oil and water)*	> 1 of 1000	postoperative
Decreased or increased intraocular pressure *(an abnormally low or high pressure in the eye often causes damage of the optic nerve)*	> 1 of 1000	postoperative
Retinal re-detachment (*detachment of the retina, possibly caused by new retinal breaks or the traction of the original tears*)	> 1 of 10000 and ≤ 1 of 1000	postoperative
Intraocular inflammations *(Inflammation in the eye)*	> 1 of 1000	postoperative
New membrane formation (*e.g. epiretinal membrane formation, macular pucker (membrane formation on the macula/retinal centre*)	> 1 of 10000 and ≤ 1 of 1000	postoperative

Side effects and complications	Expected frequency	Time of occurrence (intraoperative, postoperative)
Choroidal detachment* (*Detachment of the choroidea – middle layer between sclera and retina of the eye*)	> 1 of 1000000 and ≤ 1 of 100000*	postoperative

*Only data on the similar device Oxane Hd are available, i.e. there are no clinical data on the product Densiron® 68 / Xtra.

All the risks (side effects / complications) described in the table above correspond risks associated with vitrectomy together with the application of a heavy silicone oil tamponade such as Densiron® 68 / Xtra.
Additionally, the side effects haemorrhages and also intra- and subretinal fluids are identified in context of the state-of-the-art data. These risks are general complications that may occur when performing vitrectomy. In the state-of-the-art data and clinical data it is not described, that these side effects are directly related to the application of an endotamponade such as Densiron® 68 and Densiron® Xtra.

o Warnings and precautions for patients

- Use in pregnant women, nursing mothers and children is not recommended.
- The indwelling time of the device should be kept as short as possible and limited to the recommended duration of use. A short length of indwelling time can reduce potential side effects and complications.
- Silicone oil could migrate out of the eye and could form lesions in the conjunctiva or eyelid.
- Before Densiron® 68 / Densiron® Xtra are permitted to be instilled in the eye, any heavy liquids, e.g., perfluorocarbons of any kind, must be completely removed from the vitreous chamber.

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

To date, no incidents or recalls have been reported. Other relevant aspects of safety are not necessary.

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

o Clinical background of the device

Heavy silicone oils are used as tamponades in eye surgeries. They serve for treatment of severe cases of retinal detachment. Their density is heavier than water. So, a good tamponade effect is restricted to the inferior retina and the posterior pole.
Densiron® 68 / Xtra consists of a silicone oil and a semifluorinated alkane. The silicone oil of Densiron® Xtra has a low emulsification rate. A short injection time is a further property of this oil. Both properties are transferable to Densiron® Xtra.
Further, these devices are used to close macular holes. The macular hole closure rate depends on many factors. The type of the macular hole is one of these factors.

o The clinical evidence for the CE-marking

The heavy silicone oil tamponades Densiron® 68 and Densiron® Xtra are well tolerated and efficiently used tamponades in ophthalmic surgery.
The clinical performance and safety of Densiron® 68 and Densiron® Xtra are well documented in publications.
The Fluoron devices Densiron® 68 and Densiron® Xtra, like the heavy silicone oil device Oxane® HD used as tamponade in ophthalmic surgery, all contain a silicone oil and a semifluorinated alkane, but in different ratios resulting in different specific densities and viscosities. However, the other properties important for clinical use on the eye as a long-term tamponade remain unchanged.
The clinical evidence (safety and clinical performance) of the products Densiron® 68/Xtra is based on clinical literature data, the results of the usability evaluation and the results of the post-market surveillance data analyses.

o Safety

Based on the publications including state-of-the-art data and clinical data on treatment of retinal detachment and macular hole treatment, the clinical performance and safety of Densiron® 68/Xtra were verified.
Further, in context of the post market surveillance data analyses one new risk was identified – “turbidity / cloudiness of the silicone oil during postoperative clinical follow-up”.
The risk assessment of Densiron® was updated accordingly and resulted in the fact that the benefit still outweighs the possible risks in context of a Densiron® application. So, if the heavy silicone oils Densiron®

are applied according to the intended use as specified in the instructions for use, a safe application of these tamponades can be guaranteed.

6. Possible diagnostic or therapeutic alternatives

When considering alternative treatments, it is recommended to contact your healthcare professional who can take into account your individual situation.

o General description of therapeutic alternatives

Since 1960, researchers have tried to find adequate substitutes to replace the physical and biological functions of the vitreous body. Different currently available tamponade agents able to fulfil this function are summarised below.

Gas	Silicone oil	Heavy silicone oil
Small volumes of undiluted gas are typically used for pneumatic retinopexy, larger volumes for pars plana vitrectomy. Sulphur hexafluoride (SF_6), perfluoroethane (C_2F_6) and perfluoropropane (C_3F_8) are the most commonly used gases. SF6 exerts an effect for 1 to 2 weeks, whereas C3F8 persists for 6 to 8 weeks. Due to their very low specific gravities they have a much greater buoyancy than silicone oils. Because the effect is greatest at the upper side of the bubble, this results in a good tamponade of the upper retina, while the patient is in an upright position, but a less effective support of the lower retina. The advantage of these gases is that they are slowly removed via the blood and replaced with aqueous humour. This makes it unnecessary to perform another surgical procedure to remove the gas from the eye, as in the case of the silicone oils. These gases are used in less complicated cases due to their shorter indwelling times in the eye. Due to the fact that gases expand rapidly with any drop in air pressure, travel by plane and stay at higher elevations are contraindicated in cases where the vitreous cavity has been instilled with gas.	Silicone oils have been used to act as internal tamponades in vitreoretinal surgery procedures for more than 40 years. Their use as intra-operative tool to stabilise the retina can be adopted in difficult cases of retinal detachment such as those complicated with proliferative vitreoretinopathy, giant retinal tears, and penetrating ocular trauma. With the introduction of pars plana vitrectomy, silicone oils became also the standard medium for post-operative long-term tamponade of the vitreous body to reattach the retina. The silicone oil tamponades manufactured by Fluoron GmbH, the medical devices Siluron® 1000/2000/Xtra/5000, are also used as a tamponade in macular hole surgery. As with gas, the good tamponade effect of silicone oils is restricted to the superior retina when the patients head is in an upright position. The indwelling time for Siluron® 1000/2000/Xtra/ 5000 should be kept as short as possible and limited to at most 6 months.	Heavy silicone oils are homogenous solutions of two substances used as a single tamponade agent with improved properties. That means the advantageous characteristics of both substances (silicone oil and perfluorohexyloctane (F6H8)) are combined within the heavy silicone oils: silicone oil with higher viscosity, lower emulsification higher surface tension against water, more stable bubble and lower dispersion along with the higher specific density and better contact (F6H8). The common products belonging to the heavy silicone oil group that are available for clinical use: Densiron® 68 and Densiron® Xtra both manufactured by Fluoron GmbH and Oxane® HD by Bausch and Lomb, which are all well tolerated and efficiently used. All these heavy silicone oil tamponades contain a silicone oil and a semifluorinated alkane component, but in different ratios resulting in different specific gravities and viscosities. The heavy silicone oils are comparable to conventional silicone oil tamponades and they provide better support for the inferior retina and the posterior pole. Like silicone oils, the heavy silicone oils have good transparency and are chemically inert. Compared to standard gas or silicone oil tamponade, the heavy silicone oil tamponades are easier to apply and due to their high specific gravity offer the potential to provide adequate support, not requiring an uncomfortable prone position for postoperative maintenance. Due to their higher than water density, they are useful tamponade agents in all cases

Gas	Silicone oil	Heavy silicone oil
		where an effect on the inferior parts of the retina is required, thus stabilizing the lower retinal layer, and sealing the cracks. The indwelling time for Densiron® 68 / Densiron® Xtra should be kept as short as possible and limited to at most 3 months.

7. Suggested training for users

Densiron® 68 / Densiron® Xtra products are prepared and used exclusively by qualified personnel for intraocular surgery. They have completed a medical degree and the corresponding specialist training. The users have experience with comparable products, because silicone oil tamponades and heavy silicone oil tamponades belong to the usual aids in the field of ophthalmic surgery.