

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Susvimo 100 mg/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL solution contains 100 mg ranibizumab*.

Each vial contains 39.5 mg of ranibizumab in 0.395 mL solution. This provides a usable fill volume of 0.1 mL, which is required to deliver a single dose of 0.02 mL solution containing 2 mg of ranibizumab into the Contivue ocular implant.

*Ranibizumab is a humanised monoclonal antibody fragment produced in *E. coli* expression vector by standard recombinant DNA technology.

Excipient with known effect

Each 0.02 mL solution contains 0.002 mg polysorbate 20.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear to slightly opalescent, colourless to slightly brownish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Susvimo is indicated in adult patients for the treatment of neovascular (wet) age-related macular degeneration (nAMD) who have achieved stable disease after previously responding to intravitreal treatment with a vascular endothelial growth factor (VEGF) inhibitor medicinal product (see section 4.2).

4.2 Posology and method of administration

Susvimo is intended for continuous release into the vitreous via the Contivue implant only. The initial fill and implant procedure and implant removal procedure must be performed in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures. The implant refill-exchange procedure should be performed under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedure.

Patient selection

Treatment with Susvimo is initiated when disease stability after intravitreal anti-VEGF medicinal product is achieved as determined by the treating physician based on anatomic and/or visual parameters.

Posology

The recommended dose of Susvimo is 2 mg (0.02 mL) delivered via the Contivue implant with refill-exchange procedures administered every 24 weeks (approximately 6 months).

Susvimo must not be substituted for or with other formulations of ranibizumab.

Supplemental dosing with intravitreal ranibizumab injection

Supplemental treatment with 0.5 mg (10 mg/mL) intravitreal ranibizumab injection may be administered in the affected eye with the Contivue implant in place if clinically necessary, based on significant decrease or reduction in visual acuity and/or extensive worsening of anatomical parameters, to reduce the risk of vision loss (see section 5.1).

Refer to the full product information for 0.5 mg (10 mg/mL) intravitreal ranibizumab injection.

Duration of treatment

Duration of treatment with Susvimo should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters. If, in the physician's judgement, visual and anatomical parameters indicate that the patient is no longer benefiting from continued treatment, Susvimo refill-exchange procedures may be discontinued. The Contivue implant may be removed from the eye if deemed clinically necessary by the physician.

Implant removal and reimplantation

Implant removal may be performed at the physician's discretion, if the benefit of removal is considered to outweigh the risks of the procedure. The decision should follow a comprehensive discussion between the physician and patient about the ocular risks associated with undergoing an implant removal procedure. The benefits and risks of retaining, removing, or removing and replacing an implant are not well characterised. Refer to the device manufacturer's implant removal procedure instructions for use.

Dose (refill-exchange) interruptions

For dose (refill-exchange) interruptions related to adverse reactions see Table 1. Following a refill-exchange interruption, a refill-exchange procedure should only be performed after resolution of the adverse reaction.

Table 1 Dose (refill-exchange) interruptions for adverse reactions

Adverse reaction	Dose interruptions
Intraocular inflammation ≥ 2+ cells or flare	Withhold dose (refill-exchange) until adverse reaction is resolved
Sight threatening adverse reactions*	
Local infections of either eye	
Infectious endophthalmitis	
Severe systemic infection	Withhold dose (refill-exchange) and consider removal of the implant if visible damage to the implant is detected that may compromise its functionality or put the eye at risk of complications (for example, septum dislodgement into the implant body (see section 4.4)).
Observed damage to the implant	
	Refer to section 6.6 and to the device manufacturer's implant removal procedure instructions for use.

* Events are considered sight threatening if they are serious and either associated with unexplained vision loss of ≥ 30 letters in best-corrected visual acuity (BCVA) lasting more than one hour, require surgical intervention to prevent permanent visual loss and/or are associated with severe intraocular inflammation.

Delayed or missed doses (refill-exchange)

If a planned dose (refill-exchange) of Susvimo is missed, it should be administered as soon as possible and the subsequent refill-exchange procedure should be performed 24 weeks (approximately 6 months) thereafter.

Special populations

Elderly

No dose adjustment is required in patients ≥ 65 years of age (see sections 5.1 and 5.2).

Renal impairment

Dose adjustment is not required in patients with renal impairment (see section 5.2).

Hepatic impairment

Dose adjustment is not required in patients with hepatic impairment (see section 5.2).

Paediatric population

There is no relevant use of Susvimo in the paediatric population in the treatment of neovascular (wet) age-related macular degeneration (nAMD).

Method of administration

Susvimo is a single-dose vial for intravitreal use with the Contivue implant only.

In order to prevent medication errors, it is important to check the labels to ensure that the medicinal product being prepared and administered is Susvimo.

Susvimo should be inspected visually for particulate matter and discolouration prior to administration (see section 6.6).

Do not administer Susvimo by any route other than via the Contivue implant (e.g. not as a bolus intravitreal injection).

The initial fill and implant, and refill-exchange procedures should be performed with adequate anaesthesia under aseptic conditions to minimise the risk of intraocular infection as per standard of care.

Initial fill and implant procedure

During the initial fill and implant procedure, a 1 mL Luer Lock Tip syringe is used to withdraw all of the medicinal product from the vial through a transfer needle (not included). Air is then expelled from the syringe, and the transfer needle is removed. The initial fill needle (blue cap) is then attached to the syringe and used to fill the implant with 0.02 mL of Susvimo (ranibizumab) solution for injection immediately prior to implant insertion. Once the implant is filled, it is inserted into the eye through the pars plana.

Implant refill-exchange procedure

The Contivue implant is refilled with 0.02 mL of replacement Susvimo (ranibizumab) solution for injection via administration through the implant septum, which is covered by the conjunctiva and Tenon's capsule. A 1 mL Luer Lock Tip syringe is used to withdraw all of the medicinal product from the vial through a transfer needle (not included). Air is then expelled from the syringe, and the transfer needle is removed. The refill needle (clear cap) is attached to the syringe, and the plunger rod is pushed until all air is expelled from the syringe and the dose is adjusted to 0.1 mL. The refill needle is then inserted into the implant to exchange its contents with replacement Susvimo (ranibizumab).

Read and refer to the device manufacturer's initial fill and implant, refill-exchange and implant removal procedure Instructions for Use prior to initially filling, implanting, refilling or removing the Contivue implant.

For instructions on preparation before administration and disposal, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active or suspected ocular or periocular infections.

Active intraocular inflammation.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Educational materials

All physicians who are expected to prescribe Susvimo must ensure they have received and are familiar with the physician guide. Physicians must explain and discuss the benefits and risks of Susvimo therapy with the patient and provide them with the patient educational materials.

Bilateral treatment

In clinical trials, the majority of patients with neovascular (wet) age-related macular degeneration (nAMD) in the fellow eye received treatment with an anti-VEGF intravitreal injection and a limited number of patients received Susvimo in the fellow eye. Due to the small number of patients with bilateral treatment with Susvimo to date, the safety and efficacy of Susvimo administered in both eyes have not been established.

Implant and implant-related procedure adverse reactions

The implant and/or implant-related procedures have been associated with vitreous haemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, traumatic cataract, device (implant) dislocation, septum dislodgement and post-surgical intraocular inflammation. All of these adverse reactions were reported during the clinical trials (see section 4.8). Patients should be instructed to report signs or symptoms, if any, that could be associated with these events without delay. In some cases, these events can present asymptotically. The implant and the tissue overlying the implant flange should be examined carefully following the initial fill and implant and refill-exchange procedures to permit early medical or surgical intervention as necessary.

Strict adherence to the device manufacturer's instructions for use for the initial fill and implant procedure, refill-exchange procedure and the implant removal procedure is required to minimise procedure-related risks.

Patients should be instructed not to push on the eye, rub the eye or touch the area of the eye where the implant is located for 30 days after the implant is inserted and for 7 days following the refill.

Following an implant insertion or implant removal procedure, the patient must wear a protective eye shield, and should be instructed not to remove the eye shield until advised by their physician (see section 4.7). Patients should wear the eye shield at bedtime for at least 7 nights after surgery.

Vitreous haemorrhage

Vitreous haemorrhage may result in temporary vision loss. Vitrectomy may be needed in the case of a non-clearing vitreous haemorrhage (see section 4.2).

Patients on antithrombotic medicinal products (e.g. oral anticoagulants, acetylsalicylic acid, nonsteroidal anti-inflammatory medicinal products) may be at increased risk of vitreous haemorrhage. Antithrombotic medicinal products are recommended to be temporarily interrupted prior to the implant insertion procedure.

Strict adherence to the device manufacturer's instructions for use (e.g. appropriate pars plana laser ablation, scleral cauterisation) is required to minimise risks of vitreous haemorrhage.

Conjunctival bleb/bleb leak

A conjunctival bleb/bleb leak is an encapsulated elevation of the conjunctiva above the implant flange, which may be secondary to subconjunctival thickening or fluid. Conjunctival blebs/bleb leaks may require additional surgical and/or medical management to avoid further complications, especially if the implant septum is no longer identifiable due to the conjunctival bleb/bleb leak.

Strict adherence to the device manufacturer's instructions for use (e.g. appropriate scleral incision length, appropriate incorporation of conjunctiva and Tenon's capsule in peritomy closure, appropriate seating of the refill needle during refill-exchange procedure) is required to minimise risks of conjunctival blebs.

Conjunctival erosion

A conjunctival erosion is a full thickness degradation or breakdown of the conjunctiva in the area of the implant flange. Conjunctival erosions could be associated with an increased risk of endophthalmitis, especially if the implant becomes exposed. Surgical intervention (e.g. conjunctival/Tenon's capsule repair) should be performed in case of conjunctival erosion with or without exposure of the implant flange.

Strict adherence to the device manufacturer's instructions for use (e.g. appropriate incorporation of conjunctiva and Tenon's capsule in peritomy closure, appropriate placement of conjunctival sutures to avoid contact with the implant edge) is required to minimise risks of conjunctival erosion.

Conjunctival retraction

A conjunctival retraction is a recession or opening of the limbal and/or radial peritomy. Conjunctival retractions could be associated with an increased risk of endophthalmitis, especially if the implant becomes exposed. Surgical intervention (e.g. conjunctival/Tenon's capsule repair) should be performed in case of conjunctival retraction with or without exposure of the implant flange.

Strict adherence to the device manufacturer's instructions for use (e.g. including appropriate suturing of the conjunctiva and Tenon's capsule to the limbus) is required to minimise risks of conjunctival retraction.

Endophthalmitis

Endophthalmitis is a serious complication of ocular procedures and requires prompt treatment as per standard of care to reduce the risk of vision loss and to maximise recovery. The incidence of endophthalmitis following Contivue procedures was 1.6 %, compared to 0.6 % for intravitreal injections of ranibizumab in the ARCHWAY study (see section 4.8). The Susvimo dose (refill-exchange) should be withheld until resolution of endophthalmitis (see section 4.2).

Patients should not have an active or suspected ocular or periocular infection or severe systemic infection prior to any implant procedure. Proper aseptic technique should always be used when administering Susvimo.

Strict adherence to the device manufacturer's instructions for use (e.g. appropriate sterile controls during implant insertion or refill-exchange procedures) is required to minimise risks of endophthalmitis (see section 4.8).

Retinal tear and retinal detachment

Retinal tear and retinal detachment may result in vision loss if not promptly treated with an intervention (e.g. pneumatic retinopexy, vitrectomy or laser photocoagulation). Delay the Susvimo dose (refill-exchange) until the retinal tear or detachment has been treated (see section 4.2).

Careful evaluation of the retinal periphery by scleral indentation should be performed and any suspected areas of abnormal vitreo-retinal adhesion or retinal tears should be treated before inserting the implant in the eye. After insertion, the retinal periphery should be examined as per standard of care.

Strict adherence to the device manufacturer's instructions for use (e.g. appropriate management of vitreous prolapse after pars plana incision) is required to minimise the risks of retinal tear or retinal detachment.

Device (implant) dislocation

The device (implant) may dislocate or subluxate into the vitreous cavity or extend outside the vitreous cavity into or beyond the subconjunctival space. Device dislocation requires urgent surgical intervention if it is associated with a positive Seidel test, retinal detachment, appositional choroidal detachment, conjunctival opening with vitreous leak and implant expulsion (open globe), or the dislocated device is resting on or near the macula, to prevent vision loss. Patients should be instructed to avoid high risk activities including pushing, rubbing or touching their eye where the implant is located. The implant should be monitored per standard of care.

Strict adherence to the device manufacturer's instructions for use (e.g. appropriate scleral incision length, appropriate targeting of the pars plana during laser ablation) is required to minimise risks of implant dislocation.

Septum dislodgement

In clinical trials, a type of implant damage where the septum has dislodged into the body of the implant has been reported. A dilated slit lamp exam and/or dilated indirect ophthalmoscopy should be performed, to inspect the implant in the vitreous cavity through the pupil prior to and after the refill-exchange procedure to identify if septum dislodgement has occurred. Discontinue treatment with Susvimo following septum dislodgement and consider implant removal should the benefit of the removal procedure outweigh the risk (see section 4.2). The benefits and risks of retaining, removing, or removing and replacing an implant with a dislodged septum are not well characterised.

Strict adherence to the device manufacturer's instructions for use (e.g. appropriate handling and insertion of the refill needle into the septum (avoid twisting and/or rotation)) is required to minimise the risk of septum dislodgement.

Intraocular inflammation

There is a risk of intraocular inflammation following Contivue procedures (e.g. implantation, refill-exchange), consistent with the risks inherent to intraocular procedures. The majority of events experienced during clinical trials occurred during the first week following Contivue procedures and resolved within one month. Use peri-operative anti-inflammatory medicinal products per standard of care and by physician discretion. Patients should be instructed to report any signs or symptoms of intraocular inflammation to their physician.

Hypersensitivity

Patients should be instructed to report any signs or symptoms of potential ocular hypersensitivity to their physician.

Systemic effects

Systemic adverse events, including non-ocular haemorrhages and arterial thromboembolic events (ATEs), have been reported following intravitreal injection of VEGF inhibitors, or with Susvimo treatment (see section 4.8). Through week 96 of the ARCHWAY clinical trial, 12 patients (4.8 %) in the Susvimo arm and 4 patients (2.4 %) in the intravitreal arm experienced an APTC event, typically in the presence of pre-existing comorbidities.

Other

Magnetic Resonance Imaging (MRI) scans should be performed under specific conditions as the implant contains titanium. It is, therefore, important that patients are informed and are given an implant card which should be kept with them at all times and shown to healthcare professionals if they require an MRI scan. The device manufacturer's instructions for use for the initial fill and implant procedure provide the scan conditions to safely perform an MRI scan for a patient with this implanted device.

Information about excipients

This medicinal product contains 0.002 mg polysorbate 20 per 0.02 mL dose. Polysorbates may cause allergic reactions. Patients need to be instructed to tell their doctor if they have any known allergies.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Adjunctive use of verteporfin photodynamic therapy (PDT) and Susvimo has not been studied.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential and contraception

Women of childbearing potential should use effective contraception during treatment and for 12 months following the last dose (refill-exchange) of Susvimo.

Pregnancy

There are no data from the use of ranibizumab in pregnant women.

Studies in animals have shown reproductive toxicity. A study in pregnant cynomolgus monkeys given intravitreal ranibizumab resulted in skeletal abnormalities in foetuses (see section 5.3).

The systemic exposure to ranibizumab is low after administration via the Contivue implant, but due to its mechanism of action, Susvimo must be regarded as potentially teratogenic and embryo-foetotoxic. Therefore, Susvimo should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus. For women who wish to become pregnant and have been treated with Susvimo, it is recommended to flush the implant with preservative-free sodium chloride solution and wait at least 3 months after the implant flush before conceiving a child.

Breast-feeding

Based on very limited data, ranibizumab may be excreted in human milk at low levels. The effect of ranibizumab on a breast-fed newborn/infant is unknown. Breast-feeding is not recommended during the use of Susvimo.

Fertility

There are no data available on fertility. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with Susvimo may pose a risk to reproductive capacity (see section 5.3).

4.7 Effects on ability to drive and use machines

Susvimo, Contivue, implant-related procedures and associated examinations have a moderate influence on the ability to drive and use machines. Patients may experience temporarily reduced vision after implant insertion, refill-exchange and implant removal procedures and the associated eye examination (see section 4.8). Patients should not drive or use machines until the eye shield, used following an implant insertion or implant removal procedure, can be removed and visual function has recovered (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The safety profile of Susvimo

This safety profile includes adverse reactions related to Susvimo, Contivue, the initial fill and implant, refill-exchange and implant removal procedures.

The most frequent adverse reactions overall were conjunctival haemorrhage (72.1 %), conjunctival hyperaemia (25.6 %), iritis (25 %), eye pain (20.6 %), cataract (19.1 %), conjunctival bleb/filtering bleb leak (14.9 %), vitreous floaters (13.5 %), and headache (11.6 %).

The most frequent adverse reactions during the post-operative period (within 37 days of initial implantation) were conjunctival haemorrhage (65.9 %), conjunctival hyperaemia (21.5 %), iritis (20.8 %) and eye pain (12 %).

The most frequent serious adverse reactions overall were septum dislodgement (10.1 %), conjunctival erosion (5.2 %), endophthalmitis (2.6 %), device dislocation (1.9 %), conjunctival retraction (1.9 %), conjunctival bleb/filtering bleb leak (1.7 %), cataract (1.4 %) and retinal detachment (1.2 %).

Adverse reactions that resulted in implant removal were septum dislodgement (5 %), conjunctival erosion (1.6 %), conjunctival retraction (1.2 %), endophthalmitis (1 %) and device dislocation (0.9 %).

The safety profile of intravitreal ranibizumab injections

In the intravitreal injection arm of the ARCHWAY clinical trial (see section 5.1), the ocular adverse events in the study eye with the highest incidence were conjunctival haemorrhage (13.8 %), vitreous detachment (8.4 %), eye pain (7.8 %), dry eye (5.4 %), vision blurred (5.4 %) and eye irritation (5.4 %).

Non-ocular adverse events with the highest incidence in the intravitreal injection arm of the ARCHWAY clinical trial were nasopharyngitis (15 %), fall (9 %), urinary tract infection (8.4 %), arthralgia (6.6 %) and bronchitis (6 %); other non-ocular adverse events observed included allergic reactions* (rash (1.8 %), pruritus (0.6 %)) (2.4 %), anaemia (1.8 %), hypersensitivity (1.8 %), cough (1.8 %), and anxiety (1.2 %).

* No events for urticaria or erythema were retrieved from the data analysed for allergic reactions.

Tabulated list of adverse reactions

The safety profile of Susvimo has been evaluated in 577 patients with nAMD in clinical trials. The median duration of treatment exposure was 244 weeks (range: 1–385 weeks). The median number of procedures, including initial fills and refill-exchanges, was 10 (range: 1–21).

Adverse reactions from clinical trials (Table 2) are listed by MedDRA System Organ Class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), very rare ($< 1/10\ 000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Adverse reactions occurring in patients treated with Susvimo in clinical trials

MedDRA System organ class	Adverse reaction
Eye disorders	
Very common	Iritis ¹ Conjunctival bleb/filtering bleb leak ² Cataract ³ Vitreous floaters Conjunctival haemorrhage Conjunctival hyperaemia Eye pain
Common	Endophthalmitis Retinal detachment ⁴ Choroidal detachment Conjunctival erosion Conjunctival thinning Conjunctival retraction Conjunctival disorder Vitreous haemorrhage Scleral thinning Hypotony of eye Vitreous detachment Conjunctivitis Iris adhesions Vitritis Iridocyclitis Blepharitis Eye irritation Conjunctival oedema Retinal haemorrhage Corneal oedema Vision blurred Corneal abrasion ⁵ Corneal disorder ⁶ Eyelid ptosis Visual acuity reduced Eye pruritus Procedural pain Lacrimation increased Ecchymosis Eyelid oedema Ocular discomfort Intraocular pressure decreased Photophobia Eye discharge Hyphaema Foreign body sensation in eyes

MedDRA System organ class	Adverse reaction
Uncommon	Retinal tear Scleral hyperaemia Administration site discomfort ⁷ Foreign body in eye Suture related complication Post procedural discomfort Device material opacification ⁸ Implant site fibrosis Tenon's capsule thickening Post procedural swelling
Injury, poisoning and procedural complications	
Very common	Headache
Common	Vomiting Nausea
Product issues	
Very common	Septum dislodgement ⁹
Common	Device dislocation

¹ Iritis: includes iritis, anterior chamber flare and anterior chamber cell.

² Conjunctival bleb/filtering bleb leak: includes conjunctival bleb, conjunctival filtering bleb leak, conjunctival cyst and implant site cyst.

³ Cataract: includes cataract, cataract nuclear, cataract cortical, cataract subcapsular and cataract traumatic.

⁴ Retinal detachment: includes retinal detachment, rhegmatogenous retinal detachment and tractional retinal detachment.

⁵ Corneal abrasion: includes corneal abrasion and vital dye staining cornea present.

⁶ Corneal disorder: includes corneal disorder and corneal endothelial disorder.

⁷ Administration site discomfort: reported as refill site irritation – discomfort.

⁸ Device material opacification: reported as opacities of unknown aetiology within implant.

⁹ Septum dislodgement: a type of implant damage where the septum dislodges into the body of the implant. The incidence of septum dislodgement was calculated from implanted patients across Susvimo clinical trials.

Description of selected adverse reactions

Vitreous haemorrhage

Overall, 7.5 % (43/577) of patients in the Susvimo arm experienced vitreous haemorrhage in the study eye. The majority of affected patients (31/43) experienced Grade 1 (≤ 15 letter BCVA loss from previous visit) or Grade 2 (16-30 letter BCVA loss from previous visit) events. 10 patients and 2 patients experienced a Grade 3 (>30 letters of BCVA loss from previous visit) and Grade 4 (light perception or worse) event, respectively. Of the 43 affected patients, 40 patients experienced an event that resolved, 1 patient experienced an event that resolved with sequelae, 1 patient experienced an event that was resolving, and 2 patients experienced an event that was unresolved. 34/43 patients experienced events that resolved spontaneously without medical or surgical intervention, 4 patients required a vitrectomy.

During the post-operative period, 4.5 % (26/577) of patients experienced vitreous haemorrhage. These events were attributed to the implant procedure in all 26 patients, with 7 patients having additional contributing factors. Of the affected 26 patients, 14 experienced Grade 1 events, 5 experienced Grade 2 events, 6 experienced Grade 3 events, and 1 experienced a Grade 4 event. All these events resolved.

No patients discontinued Susvimo treatment or had their implant removed due to vitreous haemorrhage.

Conjunctival bleb/Conjunctival filtering bleb leak

Overall, 14.9 % (86/577) of patients in the Susvimo arm experienced conjunctival bleb/conjunctival filtering bleb leak in the study eye, with 5 % (29/577) of patients experiencing these events during the post-operative period. The majority of affected patients experienced mild (72/86) or moderate (10/86) events, and 4 patients experienced severe events. Of the 86 affected patients, 78 patients experienced an event that resolved, 1 patient experienced an event that resolved with sequelae, and 13 patients

experienced events that were unresolved. Overall, 8/86 patients experienced an event that required surgical intervention.

Conjunctival erosion

Overall, 8.7 % (50/577) of patients in the Susvimo arm experienced conjunctival erosion in the study eye, with 0.3 % (2/577) of patients experiencing these events during the post-operative period. The majority of affected patients experienced mild (16/50) or moderate (23/50) events, and 11 patients experienced a severe event. Surgical intervention was required for a conjunctival erosion event in 47 patients. Of the 50 affected patients, 49 patients experienced an event that resolved, while 2 patients experienced events that were unresolved. 7/50 patients discontinued Susvimo treatment due to conjunctival erosion. Implant removal was necessary in 8/50 patients due to conjunctival erosion, with 2 patients having additional contributing factors.

Conjunctival retraction

Overall, 3.5 % (20/577) of patients in the Susvimo arm experienced conjunctival retraction in the study eye, with 0.7 % (4/577) of patients experiencing these events during the postoperative period. The majority of affected patients experienced mild (9/20) or moderate (9/20) events, and 2 patients experienced a severe event. Surgical intervention was required for a conjunctival retraction event in 14 patients. Of the 20 affected patients, all patients experienced events that resolved. 6/20 patients discontinued Susvimo treatment due to conjunctival retraction. Implant removal was necessary in 6/20 patients due to conjunctival retraction, with 1 patient having additional contributing factors.

Endophthalmitis

Overall, 2.8 % (16/577) of patients in the Susvimo arm experienced endophthalmitis in the study eye. Of the affected patients, 4 patients experienced moderate events, and 12 patients experienced a severe event. Of these patients, 8/16 experienced preceding or concurrent conjunctival retraction or conjunctival erosion events. Surgical intervention was required for an endophthalmitis event in 12 patients. Of the 16 affected patients, 14 patients experienced an event that resolved, 2 patients experienced an event that resolved with sequelae, and 1 patient experienced an event that was unresolved. 8/16 patients discontinued Susvimo treatment due to endophthalmitis. Implant removal was necessary in 8/16 patients due to endophthalmitis, with 1 patient having additional contributing factors.

During the comparator period of the ARCHWAY clinical trial, the incidence of endophthalmitis was 1.6 % (4/248) in the Susvimo arm compared to 0.6 % (1/167) in the intravitreal ranibizumab arm. In clinical trials the management of endophthalmitis included a flush of implant contents with 100 µL of vancomycin (1.0 mg/0.1 mL), with or without previous flush with preservative-free sodium chloride solution, in addition to standard of care.

Retinal tear and retinal detachment

Overall, 0.7 % (4/577) of patients in the Susvimo arm experienced retinal tear in the study eye, with 0.2 % (1/577) of patients experiencing this event (mild) during the post-operative period. In the 4 affected patients, the events were mild (2 patients) and moderate (2 patients), and 2 patients experienced events that resolved, while 2 patients experienced events that were unresolved.

Overall, 1.6 % (9/577) of patients in the Susvimo arm experienced retinal detachment in the study eye, with 0.3 % (2/577) of patients experiencing these events during the post-operative period. All 9 patients with retinal detachment experienced severe events, which were managed with surgical intervention. Of the 9 affected patients, 7 patients experienced an event that resolved, 1 patient experienced an event that resolved with sequelae, 1 patient experienced an event that was unresolved, and 1 patient experienced an event that was resolving. Implant removal was necessary in 1/9 patients due to retinal detachment, this patient discontinued Susvimo treatment.

Device (implant) dislocation

Overall, 2.4 % (14/577) of patients in the Susvimo arm experienced device dislocation in the study eye. The majority of affected patients experienced mild (3/14) or moderate (6/14) events, and 5 patients experienced severe events. Surgical intervention was required for a device location event in

13 patients, including all severe cases. Of the 14 affected patients, 13 patients experienced an event that resolved and 1 patient experienced an event that was unresolved. 8/14 patients discontinued Susvimo treatment, and implant removal was necessary in 9/14 patients, due to device dislocation.

Arterial thromboembolic events

Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. Through week 96 of the ARCHWAY clinical trial, 12 patients (4.8 %) in the Susvimo arm and 4 patients (2.4 %) in the intravitreal arm experienced an APTC event, typically in the presence of pre-existing comorbidities.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system](#) listed in [Appendix V](#).

4.9 Overdose

Doses of ranibizumab as high as 2 mg have been administered via an intravitreal injection. The adverse drug reactions observed at the 2 mg intravitreal dose were consistent with those reported for the 0.5 mg intravitreal ranibizumab dose in clinical trials.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antineovascularisation agents, ATC code: S01LA04

Mechanism of action

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to all biologically active VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2.

Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, which contribute to the progression of the neovascular form of age-related macular degeneration.

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response to Susvimo. Prior to treatment with Susvimo, 2.1 % (5/243) of patients with nAMD tested positive for anti-ranibizumab antibodies. After treatment with Susvimo, 13.4 % (33/247) of patients tested positive for anti-ranibizumab antibodies.

No clinically meaningful differences in the pharmacokinetics, efficacy or safety were observed in patients testing positive for anti-ranibizumab antibodies in clinical trials.

Clinical efficacy and safety

The clinical efficacy and safety of Susvimo were assessed in a randomised, visual assessor-masked, open-label active treatment-controlled study (ARCHWAY) in patients with nAMD. A total of

415 patients (248 in the Susvimo arm and 167 in the intravitreal ranibizumab arm) were enrolled and treated in this study.

Patients were diagnosed with any type of macular choroidal neovascularisation (CNV) related to nAMD within the 9 months prior to screening and received ≥ 3 doses of anti-VEGF intravitreal agents in the study eye within the last 6 months prior to screening. At the screening visit, patients received an additional intravitreal injection of 0.5 mg ranibizumab if they received only 3 doses of anti-VEGF intravitreal agents within the last 6 months and/or if the last treatment received prior to screening was not 0.5 mg ranibizumab. Each patient had a demonstrated response to anti-VEGF intravitreal agents defined as: overall decrease in nAMD disease activity detected on spectral-domain optical coherence tomography (SD-OCT) and stable or improved vision.

Patients were randomised in a 3:2 ratio to receive continuous delivery of Susvimo via the implant every 24 weeks or intravitreal injections of 0.5 mg ranibizumab every 4 weeks. For patients randomised to the Susvimo arm, supplemental treatment with 0.5 mg intravitreal ranibizumab injections was available at weeks 16, 20, 40, 44, 64, 68, 88, and 92 if one of the following criteria was met and due to nAMD disease activity: a loss of 15 early treatment diabetic retinopathy study (ETDRS) letters from the best recorded BCVA value on study, an increase of 150 microns from the lowest central subfield thickness (CST) value on study, or a loss of 10 letters from the highest BCVA value associated with an increase of 100 microns from the lowest CST value.

The baseline demographics were generally balanced across treatment groups; 43/415 (10.4%) patients were younger than 65 years of age and the mean [SD] age was 75 [7.91] years. The majority of patients were female (59 %). The mean [SD] BCVA score at baseline was 74.8 [10.4] letters.

Prior to study treatment, a median of 4 doses of anti-VEGF intravitreal agents were administered in the study eye of the patients in the Susvimo and intravitreal ranibizumab arms. The mean [SD] change in visual acuity in the study eye from diagnosis of nAMD to baseline was 11.3 [13.8] letters. Of the patients assessed for supplemental treatment in the Susvimo arm, 98.4 %, 94.6 %, 94.8 % and 94.7 % did not receive supplemental treatment in the first, second, third and fourth treatment intervals, respectively. Across all four treatment intervals, 31/246 patients (12.6%) received supplemental treatment, and 215/246 patients (87.4%) did not receive supplemental treatment. Of the 31 patients, 18 patients (58.1%) received only one supplemental treatment.

The primary efficacy endpoint of change from baseline in BCVA score averaged over week 36 and week 40 demonstrated Susvimo to be equivalent to intravitreal ranibizumab injections administered every 4 weeks. Detailed efficacy results are shown in Table 3 and Figure 1.

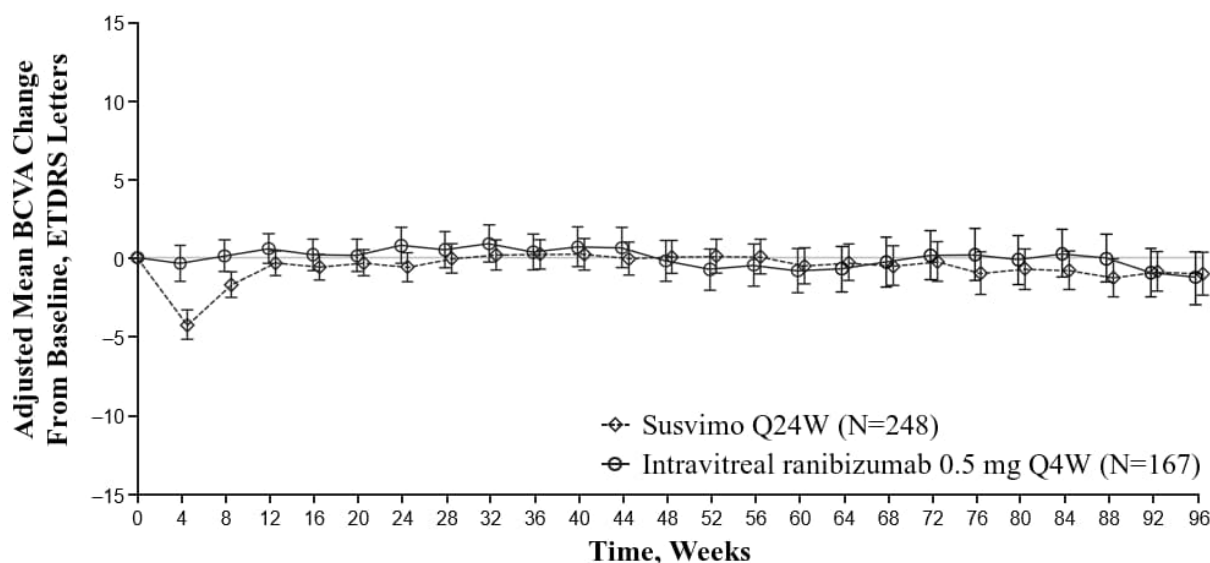
Table 3 Visual acuity outcomes in the ARCHWAY study

Outcome measure*	Susvimo 100 mg/mL n = 248	Intravitreal ranibizumab 0.5 mg n = 167	Difference (95 % CI)
Adjusted mean change from baseline in BCVA score averaged over weeks 36 and 40	0.2	0.5	-0.3 (-1.7, 1.1)
Adjusted mean change from baseline in BCVA score averaged over weeks 44 and 48	0.0	0.2	-0.2 (-1.8, 1.3)
Adjusted mean change from baseline in BCVA score averaged over weeks 88 and 92	-1.1	-0.5	-0.6 (-2.5, 1.3)
Adjusted proportion of patients with BCVA score of 69 letters (20/40 approximate Snellen equivalent) or better averaged over weeks 36 and 40	80.7 %	82.1 %	-1.4 % (-7.3 %, 4.5 %)
Adjusted proportion of patients who lose < 10 letters in BCVA score from baseline averaged over weeks 36 and 40	95.1 %	95.1 %	0.0 % (-4.2 %, 4.3 %)

BCVA = Best-corrected visual acuity.

* BCVA measured by ETDRS letters score.

Figure 1 Adjusted mean change from baseline in BCVA in study eye through week 96 in the ARCHWAY study*



Q24W = every 24 weeks; Q4W = every 4 weeks.

*Decrease in BCVA at week 4 during post-operative recovery.

Consistent results were observed across patient subgroup analyses for mean change from baseline in BCVA score averaged over weeks 36 and 40 (age, gender, number of prior anti-VEGF intravitreal injections and baseline BCVA score) and centre point thickness (CPT) at week 36 (age and gender).

Leakage of blood and fluid from CNV may cause retinal thickening or oedema and/or intraretinal/subretinal haemorrhage, resulting in vision loss. The anatomical parameter CPT [measured from internal limiting membrane (ILM) to retinal pigment epithelium] was assessed. At week 36, a similar adjusted mean change in CPT was observed between the Susvimo arm and intravitreal ranibizumab arm patients (5.4 microns vs 2.6 microns, respectively). This corresponded to a difference in adjusted means of 2.8 microns (95 % CI: -6.2, 11.8) between arms.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Susvimo in all subsets of the paediatric population for nAMD (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Susvimo delivered via the Contivue implant provides continuous delivery of ranibizumab into the vitreous, with the release of ranibizumab decreasing over time as the concentration in the implant decreases. The observed serum and observed aqueous humour ranibizumab concentrations with Susvimo are maintained below the maximum and above the minimum concentrations achieved with monthly 0.5 mg intravitreal ranibizumab.

In the ARCHWAY clinical trial, the mean ($\pm$ SD) maximum ranibizumab serum concentration (C_{max}) was 0.48 ($\pm$ 0.17) ng/mL and median (range) time to maximum serum concentration (T_{max}) was 26 (1 – 89) days following implant insertion. Following the initial fill and refill-exchange procedures with Susvimo in patients with nAMD, maximum serum concentrations of ranibizumab were below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50 %.

Distribution

Ranibizumab is distributed from the vitreous to the aqueous humour and serum. Based on population pharmacokinetics analysis, the ranibizumab concentrations in aqueous humour decrease with a half-life of approximately 15 weeks and the ranibizumab serum concentrations decrease with a half-life of approximately 29 weeks. Ranibizumab did not accumulate in serum when administered with refill-exchange procedures every 24 weeks.

Biotransformation and elimination

The metabolism of Susvimo has not been directly studied. Susvimo is a monoclonal antibody fragment. Antibodies are cleared principally by catabolism.

Special populations

Elderly

In the population pharmacokinetic analysis of nAMD patients with Susvimo, the age of patients ranged from 50 to 92 years old. Age did not have a significant effect on the pharmacokinetics of Susvimo.

Renal impairment

No formal studies have been conducted to examine the pharmacokinetics of Susvimo in patients with renal impairment. In a population pharmacokinetic analysis of nAMD patients with Susvimo, 73 % (266 of 364) had renal impairment (44 % mild [CrCL 60 to < 90 mL/min], 27 % moderate [CrCL 30 to < 60 mL/min] and 2 % severe [CrCL < 30 mL/min]). This analysis showed that systemic clearance of ranibizumab was slightly lower in renally impaired patients but was not clinically significant.

Hepatic impairment

No formal studies have been conducted to examine the pharmacokinetics of Susvimo in patients with hepatic impairment. However, systemic exposure of Susvimo is low, with concentrations remaining below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50 % (11-27 ng/mL). Therefore, no dose adjustment is considered necessary in this population (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on findings via intravitreal injection in cynomolgus monkeys or continuous delivery via the ocular implant in minipigs. Observed ocular effects (inflammation, cataracts, fibrosis, retinal detachment, optic nerve traction, swelling and photoreceptor nuclei drop down) were attributed to species-specific immune responses to the heterologous protein (evidenced by systemic anti-ranibizumab antibodies) and are not considered relevant to clinical use.

Carcinogenicity and genotoxicity

No studies have been performed to establish the carcinogenic or mutagenic potential of Susvimo.

Impairment of fertility

No fertility studies in animals have been performed to evaluate the effect of ranibizumab.

Although no effects on reproductive tissues were noted in repeat-dose monkey studies with intravitreal ranibizumab, inhibition of VEGF in human female reproductive tissues could potentially impair fertility.

Reproductive toxicity

No reproductive and developmental toxicity studies have been conducted with Susvimo (ranibizumab delivered via the Contivue implant).

In pregnant monkeys treated with intravitreal ranibizumab throughout the period of organogenesis, skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with doses resulting in trough serum ranibizumab levels up to 18-times higher than observed human C_{max} levels after treatment of a single eye with Susvimo. However, due to its mechanism of action, Susvimo must be regarded as potentially teratogenic and embryo-fetotoxic (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine hydrochloride
Polysorbate 20 (E 432)
Sucrose
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Prior to use, the unopened vial may be kept at 9 °C to 30 °C for up to 24 hours.

6.5 Nature and contents of container

Type I borosilicate glass 2 mL vial with a fluororesin-laminated rubber stopper and an aluminium seal with a plastic flip off cap.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Read and refer to the appropriate device manufacturer's instructions for use for initial fill and implant, refill-exchange, and implant removal procedures prior to filling, implanting, refilling or removing the Contivue implant.

The solution should be inspected visually for particulate matter and discolouration prior to administration. Susvimo is a clear to slightly opalescent, colourless to slightly brownish solution. Do not use the medicinal product if it has particulate matter, cloudiness or discolouration.

Do not shake the solution.

Initial fill and implant procedure

Devices necessary for administration:

- Transfer needle (19-gauge, 1½ inch) (not included)
- Luer lock syringe (1 mL, Luer Lock Tip) (not included)
- Contivue initial fill needle
- Contivue implant with insertion tool assembly

Using aseptic technique, the implant is filled with 0.02 mL of Susvimo (ranibizumab) solution for injection immediately prior to insertion into the patient's eye. The following instructions should be followed to prepare the syringe:

1. Transfer dose from vial to syringe
Attach the transfer needle to the Luer Lock syringe, remove the needle cap, and use it to withdraw all of the contents of the Susvimo vial into the syringe.
2. Remove air from syringe
Holding the syringe with the needle pointing up, gently tap the syringe with your finger until any bubbles rise to the top. Slowly push the plunger rod until all air is expelled from the syringe and needle, preserving as much Susvimo solution as possible in order to completely fill the implant. Remove and properly dispose of the transfer needle.
3. Attach initial fill needle (blue cap)
Attach the initial fill needle to the Luer Lock syringe and remove the needle cap. Remove air from the syringe, as described in step 2 above, and ensuring that when the plunger rod is pushed, a drop of Susvimo solution is seen at the needle tip.
4. Inspect the syringe for air bubbles
Inspect the syringe and the needle hub to ensure that no air bubbles are present. If air bubbles are present, continue to remove air from the syringe, as described above, and reinspect.

The syringe is now ready to load into the insertion tool assembly and fill the implant with Susvimo solution. Use the syringe within **15 minutes** of removing all air to avoid the Susvimo solution drying in the needle and impeding fluid flow.

Once the implant is filled, do not recap the initial fill needle or detach it from the syringe. Dispose of the used syringe together with the initial fill needle in a sharps disposal container or in accordance with local requirements.

Implant refill-exchange procedure

Devices necessary for administration:

- Transfer needle (19-gauge, 1½ inch) (not included)
- Luer lock syringe (1 mL, Luer Lock Tip) (not included)
- Contivue refill needle

The implant contents will be extracted simultaneously as the implant is filled with 0.02 mL of replacement Susvimo (ranibizumab) solution for injection, using aseptic technique. The following instructions should be followed to prepare the syringe:

1. Transfer dose from vial to syringe
Attach the transfer needle to the Luer Lock syringe, remove the needle cap, and use it to withdraw all of the contents of the Susvimo vial into the syringe.

2. Remove air from syringe

Holding the syringe with the needle pointing up, gently tap the syringe with your finger until any bubbles rise to the top. Slowly push the plunger rod until all air is expelled from the syringe and needle, preserving as much Susvimo solution as possible in order to completely fill the implant. Remove and properly dispose of the transfer needle.

3. Attach refill needle (clear cap)

Attach the refill needle to the Luer Lock syringe and remove the needle cap.

4. Remove air from syringe and adjust dose

Remove air from the syringe, as described in step 2 above. Slowly push the plunger rod until all air is expelled from the syringe and needle and the dose of Susvimo solution in the syringe is adjusted to 0.1 mL.

5. Inspect the syringe for air bubbles

Inspect the syringe and the needle hub using magnification to ensure that no air bubbles are present.

The syringe is now ready for the refill-exchange procedure. Use the syringe within **15 minutes** of removing all air to avoid the Susvimo solution drying in the needle and impeding fluid flow.

Once the implant contents are exchanged, do not recap the refill needle or detach it from the syringe. Dispose of the used syringe together with the refill needle in a sharps disposal container or in accordance to local requirements.

The contents of the vial and the initial fill and refill needles are supplied sterile and for single use only. Do not reprocess, re-sterilise or re-use any component. Do not use any component if it is damaged, broken or the sterility has been compromised.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2058/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR
BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL
PRODUCT**

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND
MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer of the biological active substance

Roche Singapore Technical Operations Ltd.
10 Tuas Bay Link
Singapore 637394

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING
AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures**

Prior to the launch of Susvimo in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the final educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall provide information on implant insertion procedure, implant removal procedure and refill-exchange procedure to ophthalmologists experienced in vitreoretinal surgery, with the aim to establish consistency in following the instructions for use and confidence in the surgical procedures associated with Susvimo. The refill-exchange procedure information will also be provided to ophthalmologists who will perform the refill-exchange procedure for Susvimo. The MAH shall also provide patient educational materials.

The MAH shall ensure that, following discussions and agreements with the National Competent Authority in each Member State where Susvimo is marketed, at launch and after launch, all ophthalmological clinics where Susvimo is expected to be used are provided with an up-to-date physician guide.

The physician guide will contain the following elements:

- Physician information
- Instruction video and pictograms on vitreoretinal surgery and performing the port delivery system (PDS) procedures
- Patient guide

The physician information will include the following key elements:

- Sterile techniques to minimise risk of infection
- Techniques for the vitreoretinal surgery and performing the PDS procedures
- Patient monitoring after the vitreoretinal surgery and the PDS procedures
- Key signs and symptoms of vitreoretinal surgery related adverse events
- Management of adverse events related to vitreoretinal surgery and performing the PDS procedures

The patient educational materials are provided in written and audio format, and will include the following key elements:

- How to prepare for Susvimo treatment
- What are the steps following treatment with Susvimo
- Key signs and symptoms of serious adverse events including endophthalmitis
- When to seek urgent attention from the health care provider

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Susvimo 100 mg/mL solution for injection
ranibizumab

2. STATEMENT OF ACTIVE SUBSTANCE

One vial contains 39.5 mg of ranibizumab in 0.395 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine hydrochloride, polysorbate 20, sucrose, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

39.5 mg/0.395 mL

1 vial

Single dose: 2 mg/0.02 mL

5. METHOD AND ROUTE OF ADMINISTRATION

Intravitreal use

Single use only

Read the package leaflet before use

For use with Contivue implant only

Do not shake

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

Do not freeze

Keep the vial in the outer carton in order to protect from light

Prior to use, the unopened vial may be kept at 9 °C to 30 °C for up to 24 hours

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Roche Registration GmbH

Emil-Barell-Strasse 1

79639 Grenzach-Wyhlen

Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/26/2058/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC

SN

NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS VIAL
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Susvimo 100 mg/mL injection
ranibizumab
Intravitreal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

39.5 mg/0.395 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Susvimo 100 mg/mL solution for injection ranibizumab

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine -because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, your doctor will give you a patient guide which contains important information that you need to be aware of.

What is in this leaflet

1. What Susvimo is and what it is used for
2. What you need to know before you are given Susvimo
3. How Susvimo is given
4. Possible side effects
5. How to store Susvimo
6. Contents of the pack and other information

1. What Susvimo is and what it is used for

What Susvimo is

Susvimo is a medicine that contains the active substance ranibizumab. This belongs to a group of medicines called 'anti-neovascularisation agents'.

Susvimo is released into the eye using an eye (ocular) implant.

What Susvimo is used for

Susvimo is used to treat adults with neovascular (wet) age-related macular degeneration (nAMD), who have responded to medicine that attaches to and blocks 'vascular endothelial growth factor' (VEGF). nAMD happens when:

- tiny, abnormal blood vessels grow in the back of the eye (retina).
- these blood vessels leak blood or fluid in the middle part of the retina (the macula) that gives you sharp detailed vision.
- these blood vessels and their bleeding can eventually form scars that can lead to permanent blind spots in the centre of your vision.

How Susvimo works

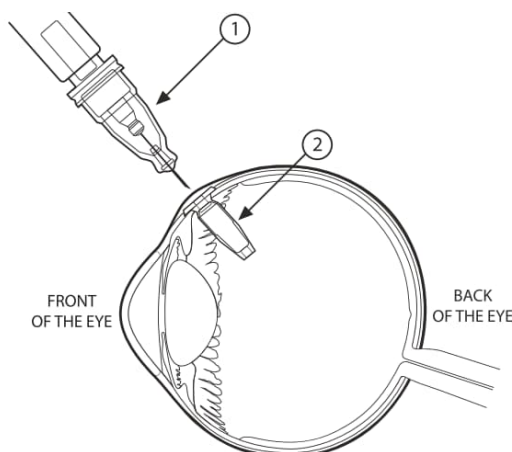
Susvimo works by attaching to and blocking 'VEGF', a protein that can cause the growth of abnormal blood vessels in your eye. This medicine stops or slows the growth and leaking of these blood vessels.

Susvimo can help maintain and in some cases, improve your vision.

The medicine is gradually released from the implant into the back of your eye. The implant is inserted in the eye with surgery, and is about the size of a grain of rice. It is filled and refilled with Susvimo by your doctor.

Where the implant is placed

The diagram below shows the refill needle (1) and the implant position in the eye (2). This diagram is not to scale.



2. What you need to know before you are given Susvimo

Before you start treatment with Susvimo, it is important that you and your doctor have discussed the benefits you could expect to receive from this treatment and the risks that are associated with it.

You must not be given Susvimo

- if you are allergic (hypersensitive) to ranibizumab or any of the other ingredients of this medicine (listed in section 6).
- if you have or think you have an infection in or around your eye.
- if you have an inflamed eye - indicated by pain or redness.

You must not be given Susvimo if any of the above apply to you. If you are not sure, talk to your doctor before having Susvimo.

Warnings and precautions

Tell your doctor immediately if you have any of these signs during treatment with Susvimo. You may need urgent medical or surgical treatment, or a delay before your next refill:

- more moving spots or “spider webs” in your vision (vitreous haemorrhage).
- a sudden feeling that something is in your eye, eye discharge or watering (conjunctival bleb / conjunctival bleb leak / conjunctival erosion / conjunctival retraction).
- worsening eye pain or vision loss, sensitivity to light or redness in the white of the eye (endophthalmitis).
- flashing lights, a change or loss of vision (retinal tear or detachment).
- clouding of the lens due to injury (traumatic cataract).
- the implant has moved out of place (device dislocation).

If you get any of the side effects listed above, tell your doctor immediately. You may need urgent medical or surgical treatment, or a pause before your next refill. See section 4, 'Possible side effects'.

It is also important for you to know that the safety and efficacy of Susvimo when given in both eyes has not been studied.

The systemic use of VEGF inhibitors is potentially related to the risk of blood clots blocking blood vessels (arterial thromboembolic events) which may lead to heart attack or stroke, especially if you have certain existing medical conditions.

Monitoring and care during your treatment with Susvimo

Your doctor will monitor your illness and the condition of the implant throughout your treatment with this medicine, to make sure they can quickly give medical assistance if needed. Follow your doctor's instructions for how to care for the treated eye to allow the eye to heal. These instructions include, but are not limited to:

After the surgery to insert the implant

- Keep your head above shoulder level for the rest of the day.
- Sleep with your head raised on 3 or more pillows when lying down, that day and night.
- Do not remove the eye shield from the eye, until you are told to by your doctor. At bedtime, continue to wear the eye shield for at least 7 nights after the surgery.
- Take all eye medicines your doctor tells you to.
- Do not push on the eye, rub the eye or touch the area of the eye where the implant is located (for example underneath the eyelid in the upper and outer part of your eye) for 30 days after the implant is inserted.
- Do not participate in strenuous activities, such as running or lifting weights, until 1 month after the implant is inserted, or until your doctor says you can.

Patient implant card and Magnetic Resonance Imaging (MRI) scan

- Get the patient implant card from your doctor and keep this card in a safe place for future reference - it has important information about the implant.
- If you need to have an MRI scan, show your healthcare providers the implant card that you have been given.
- You can only have an MRI scan under very specific conditions.

After the refill procedure

- Do not push on the eye, rub the eye or touch the area of the eye where the implant is located (for example underneath the eyelid in the upper and outer part of your eye) for 7 days following the refill.
- Take all eye medicines your doctor tells you to.

After the implant removal procedure (if removal is deemed medically necessary)

- Keep your head above shoulder level for the rest of the day.
- Sleep with your head raised on 3 or more pillows when lying down that day and night.
- Wear an eye shield for at least 7 nights following the removal.
- Do not participate in strenuous activities, such as running or lifting weights, until 14 days after the implant removal procedure.
- Take all eye medicines your doctor tells you to.

Throughout treatment with Susvimo

- Do not rub your eye, or touch the area of your eye where the implant is, as much as possible. If you need to, make sure you clean your hands before touching your eye.

Implant damage

During your treatment with Susvimo, the implant may become damaged. If this damage prevents the proper filling of the implant, your nAMD may be inadequately treated and your physician may remove the implant from your eye and/or change your treatment.

Children and adolescents

Susvimo has not been studied in children and adolescents, because nAMD only happens in adults.

Other medicines and Susvimo

Before you receive Susvimo, tell your doctor if you are taking, have recently taken or might take any other medicines.

In particular tell your doctor if you are taking any of the following medicines, as their use would be an important consideration for surgery:

- medicines that reduce the formation of blood clots, such as warfarin or low dose acetyl salicylic acid.
- nonsteroidal anti-inflammatory medicines, such as ibuprofen or naproxen.

If any of the above apply to you (or you are not sure), talk to your doctor before you are given Susvimo.

Contraception

Women who could become pregnant should use effective contraception:

- when being given this medicine, and
- for at least 12 months after the last time the implant was refilled.

Pregnancy and breast-feeding

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine. There is no information currently available about using this medicine when you are pregnant. This medicine could harm an unborn baby. If you become pregnant during treatment, your doctor may replace the medicine with preservative-free sodium chloride solution in the implant. Your doctor will discuss this with you. They will only continue your treatment with this medicine if the potential benefits to you outweighs the potential risks to your unborn baby.
- Do not use this medicine while you are breast-feeding because it is not known whether Susvimo passes into human milk. Ask your doctor for advice before treatment.

Driving and using machines

You may have worse vision for a while after the implant is inserted, removed, refilled with medicine, or after eye examinations.

Do not drive or use machines until your doctor tells you to remove the eye shield - and the reduced vision is better.

Susvimo contains polysorbate 20

This medicine contains 0.002 mg polysorbate 20 per 0.02 mL dose. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How Susvimo is given

Before you are given Susvimo your doctor will check that you respond to medicine that attaches to and blocks 'VEGF'.

How much and how often Susvimo is given

- The recommended dose is 2 mg given gradually by the implant.
- The implant is refilled every 24 weeks - roughly 6 months - by your doctor.

Based on how you respond to treatment with Susvimo, your doctor may give additional injections into your eye in the 24-week refill period.

How you will be given Susvimo

An eye surgeon trained in the implant procedures will fill the implant with Susvimo before inserting the implant in your eye. After, the implant will be refilled by your eye doctor (trained in the refill procedure) at regular times.

- Your doctor(s) will inject medicine, to numb the eye for both of these procedures.
- Your doctor will perform an aseptic or sterile procedure to reduce the risk of infection. See section 2 'Monitoring and care during your treatment with Susvimo'.

Susvimo must only be given using the implant meant for this medicine.

How long you will keep the implant

The implant is intended to remain in the eye, unless removed for medical reasons. Your doctor will keep track of your illness to check the treatment is working properly. They may need to stop the refills of Susvimo or safely remove the implant using surgery (if medically necessary).

If you miss a dose (refill) of Susvimo

If you miss a refill, book a new appointment with your doctor to get the refill as soon as possible. Do not wait until the next planned refill.

Before stopping treatment with Susvimo

If you are considering stopping Susvimo, make sure you discuss this with your doctor, as they will need to discuss with you about monitoring your eye and the need to retain or remove the implant. Your doctor will discuss other treatments to determine the best one for you. Stopping all treatment may increase your risk of vision loss and your vision may get worse.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The list of possible side effects includes those related to Susvimo, the implant in the eye and the procedures to place, refill and remove the implant.

Some side effects may be serious

Tell your doctor **immediately** if you notice any of the following serious side effects – you may need urgent medical or surgical treatment, or a delay before your next refill:

Very common: may affect more than 1 in 10 people.

Common: may affect up to 1 in 10 people.

Uncommon: may affect up to 1 in 100 people.

- more moving spots or “spider webs” in your vision. You may have bleeding in the gel-like substance at the back of the eye (vitreous haemorrhage) - common
- a sudden feeling that something is in your eye, eye discharge or watering. This feeling may mean:
 - a small bulge in the layer that covers the white part of the eye (conjunctival bleb) - very common
 - fluid leaking creating a blister-like bulge on the surface of the eye (conjunctival bleb leak) - very common
 - the layer that covers the white part of your eye is wearing away (conjunctival erosion), which can expose the implant - common
 - stitches are opening to make a gap in the layer that covers the white of the eye (conjunctival retraction). This could expose the implant - common
- worsening eye pain with vision loss, sensitivity to light, or redness in the white of the eye. This might be an infection of the eyeball with inflammation inside of the eye (endophthalmitis) - common
- flashing lights, a change or loss of vision. This may mean:
 - You have a hole or tear in the layer (the retina) in the back of the eye that senses light (retinal tear) - uncommon
 - You have separation of the layer (the retina) in the back of the eye where light is sensed (retinal detachment) - common
- clouding of the lens of the eye due to injury (traumatic cataract) - uncommon
- the implant has moved out of place (device dislocation) - common

If you notice any of the serious side effects above, tell your doctor immediately.

Other side effects

Most of the side effects are mild to moderate.

Tell your doctor if any of the following side effects become severe:

Very common: may affect more than 1 in 10 people

- blood in the layer that covers the white of the eye (conjunctival haemorrhage)
- redness in the layer that covers the white of the eye (conjunctival hyperaemia)
- inflammation of the coloured part of the eye (iritis)
- eye pain
- clouding of the lens of the eye (cataract)
- moving spots in the vision (vitreous floaters)
- headache
- implant damage

Common: may affect up to 1 in 10 people

- bleeding at the back of the eye
- sensation that something is in the eye
- eye irritation or discomfort - burning, stinging, itching, tearing, redness
- nausea, vomiting
- lowered pressure inside the eye

- when the gel-like substance at the back of the eye (vitreous) shrinks and separates from the layer (retina) at the back of the eye that senses light (vitreous detachment)
- vision blurred or less sharp
- swelling of the eyelid, clear part at the front of the eye or the layer that covers the white part of the eye
- inflammation of the eyelid - redness, pain, swelling and itching of the eyelids or eyelid scales
- scratched eye surface (corneal abrasion)
- drooping of the upper eyelid
- itchy eyes
- thinning of the white part of the eye
- defect of the clear part (cornea) at the front of the eye
- eye discharge, increased production of tears, or watering eyes
- eyes feeling more sensitive to light
- infection of the layer that covers the white of the eye (conjunctivitis)
- pain during the procedure
- inflammation of the gel-like substance at the back of the eye (vitritis)
- separation of the layer of blood vessels from underneath the white part of the eye (choroidal detachment)
- bruising around the eye following surgery
- blood in front of the coloured part (the iris) of the eye
- inflammation of the coloured part of the eye (the iris) and its nearby tissue
- thinning of the layer that covers the white part of the eye
- attachment of the coloured part of the eye (the iris) to other structures in the eye (iris adhesions)
- defect of the layer that covers the white part of the eye

Uncommon: may affect up to 1 in 100 people

- cloudiness of the implant
- redness in the white part of the eye
- exposed stitches – or other problems after the implant procedure
- discomfort after a refill at or near where the implant is, or discomfort after the procedure
- scar tissue formation where the implant was inserted (fibrosis)
- a reaction (for example swelling) at or near where the implant is
- foreign object in the eye
- swelling after the procedure

If any of these side effects become severe, please tell your doctor.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Susvimo

The following information is intended for healthcare professionals.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Prior to use, the unopened vial may be kept at 9 °C to 30 °C for up to 24 hours.

6. Contents of the pack and other information

What Susvimo contains

- The active substance is ranibizumab. One mL of solution contains 100 mg ranibizumab. Each vial contains 39.5 mg ranibizumab in 0.395 mL solution.
- The other ingredients are: histidine hydrochloride, polysorbate 20 (E 432), sucrose, water for injections.

See ‘Susvimo contains polysorbate 20’ in section 2 for more information.

What Susvimo looks like and contents of the pack

Susvimo 100 mg/mL solution for injection (injection) is a clear to slightly opalescent (a pearl like shine), colourless to slightly brownish solution.

Each carton of Susvimo contains one glass vial.

Marketing Authorisation Holder

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

Manufacturer

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien,
Luxembourg/Luxemburg**
N.V. Roche S.A.
België/Belgique/Belgien
Tél/Tel: +32 (0) 2 525 82 11

Latvija
Roche Latvija SIA
Tel: +371 - 6 7039831

България
Рош България ЕООД
Тел: +359 2 474 5444

Lietuva
UAB “Roche Lietuva”
Tel: +370 5 2546799

Česká republika
Roche s. r. o.
Tel: +420 - 2 20382111

Magyarország
Roche (Magyarország) Kft.
Tel: +36 - 1 279 4500

Danmark
Roche Pharmaceuticals A/S
Tlf.: +45 - 36 39 99 99

Nederland
Roche Nederland B.V.
Tel: +31 (0) 348 438000

Deutschland

Roche Pharma AG
Tel: +49 (0) 7624 140

Eesti

Roche Eesti OÜ
Tel: + 372 - 6 177 380

Ελλάδα, Κύπρος

Roche (Hellas) A.E.
Ελλάδα
Τηλ: +30 210 61 66 100

España

Roche Farma S.A.
Tel: +34 - 91 324 81 00

France

Roche
Tél: +33 (0)1 47 61 40 00

Hrvatska

Roche d.o.o.
Tel: + 385 1 47 22 333

Ireland, Malta

Roche Products (Ireland) Ltd.
Ireland/L-Irlanda
Tel: +353 (0) 1 469 0700

Ísland

Roche Pharmaceuticals A/S
c/o Icepharma hf
Sími: +354 540 8000

Italia

Roche S.p.A.
Tel: +39 - 039 2471

Norge

Roche Norge AS
Tlf: +47 - 22 78 90 00

Österreich

Roche Austria GmbH
Tel: +43 (0) 1 27739

Polska

Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

Portugal

Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

România

Roche România S.R.L.
Tel: +40 21 206 47 01

Slovenija

Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

Slovenská republika

Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland

Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige

Roche AB
Tel: +46 (0) 8 726 1200

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<https://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

How to prepare and administer Susvimo

Single-dose vial for intravitreal use with the Contivue implant (provided separately). Do not administer Susvimo by any route other than via the Contivue implant (e.g. not as a bolus intravitreal injection).

Do not substitute Susvimo for or with other formulations of ranibizumab.

The solution should be inspected visually for particulate matter and discolouration prior to administration. Susvimo is a clear to slightly opalescent, colourless to slightly brownish solution. Do not use the medicine if it has particulate matter, cloudiness or discolouration.

The initial fill and implant procedure and implant removal procedure must be performed by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures. The implant refill-exchange procedure should be performed by an ophthalmologist trained in the implant refill-exchange procedure.

Read and refer to the instructions for use provided by the implant device manufacturer prior to initially filling, implanting, refilling or removing the Contivue implant.

Do not prepare the medicine until you are ready to start the initial fill and implant procedure or refill-exchange procedure.

The initial fill and implant, and refill-exchange procedures should be performed with adequate anaesthesia under aseptic conditions to minimise the risk of intraocular infection as per standard of care.

Initial fill and implant procedure

Devices necessary for administration:

- Transfer needle (19-gauge, 1½ inch) (not included)
- Luer lock syringe (1 mL, Luer Lock Tip) (not included)
- Contivue initial fill needle
- Contivue implant with insertion tool assembly

Using aseptic technique, the implant is filled with 0.02 mL of Susvimo (ranibizumab) solution for injection immediately prior to insertion into the patient's eye. The following instructions should be followed to prepare the syringe:

1. Transfer dose from vial to syringe

Attach the transfer needle to the Luer Lock syringe, remove the needle cap, and use it to withdraw all of the contents of the Susvimo vial into the syringe.

2. Remove air from syringe

Holding the syringe with the needle pointing up, gently tap the syringe with your finger until any bubbles rise to the top. Slowly push the plunger rod until all air is expelled from the syringe and needle, preserving as much Susvimo solution as possible in order to completely fill the implant. Remove and properly dispose of the transfer needle.

3. Attach initial fill needle (blue cap)

Attach the initial fill needle to the Luer Lock syringe and remove the needle cap. Remove air from the syringe, as described in step 2 above, and ensuring that when the plunger rod is pushed, a drop of Susvimo solution is seen at the needle tip.

4. Inspect the syringe for air bubbles

Inspect the syringe and the needle hub to ensure that no air bubbles are present. If air bubbles are present, continue to remove air from the syringe, as described above, and reinspect.

The syringe is now ready to load into the insertion tool assembly and fill the implant with Susvimo solution. Use the syringe within **15 minutes** of removing all air to avoid the Susvimo solution drying in the needle and impeding fluid flow.

Once the implant is filled, it is inserted into the eye through the pars plana. Do not recap the initial fill needle or detach it from the syringe. Dispose of the used syringe together with the initial fill needle in a sharps disposal container or in accordance with local requirements.

Implant refill-exchange procedure

Devices necessary for administration:

- Transfer needle (19-gauge, 1½ inch) (not included)
- Luer lock syringe (1 mL, Luer Lock Tip) (not included)
- Contivue refill needle

The implant contents will be extracted simultaneously as the implant is filled with 0.02 mL of replacement Susvimo (ranibizumab) solution for injection, using aseptic technique. The following instructions should be followed to prepare the syringe:

1. Transfer dose from vial to syringe

Attach the transfer needle to the Luer Lock syringe, remove the needle cap, and use it to withdraw all of the contents of the Susvimo vial into the syringe.

2. Remove air from syringe

Holding the syringe with the needle pointing up, gently tap the syringe with your finger until any bubbles rise to the top. Slowly push the plunger rod until all air is expelled from the syringe and needle, preserving as much Susvimo solution as possible in order to completely fill the implant. Remove and properly dispose of the transfer needle.

3. Attach refill needle (clear cap)

Attach the refill needle to the Luer Lock syringe and remove the needle cap.

4. Remove air from syringe and adjust dose

Remove air from the syringe, as described in step 2 above. Slowly push the plunger rod until all air is expelled from the syringe and needle and the dose of Susvimo solution in the syringe is adjusted to 0.1 mL.

5. Inspect the syringe for air bubbles

Inspect the syringe and the needle hub using magnification to ensure that no air bubbles are present.

The syringe is now ready for the refill-exchange procedure. Use the syringe within **15 minutes** of removing all air to avoid the Susvimo solution drying in the needle and impeding fluid flow.

Once the implant contents are exchanged, do not recap the refill needle or detach it from the syringe. Dispose of the used syringe together with the refill needle in a sharps disposal container or in accordance with local requirements.