PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] SUSVIMO™

ranibizumab injection

Single-use vials

100 mg/mL sterile solution for intravitreal use via SUSVIMO ocular implant

Ophthalmological / Anti-Vascular Endothelial Growth Factor-A agent

ATC Code: S01LA04

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Date of Initial Authorization:
SEPT 14, 2022

Submission Control Number: 254848

RECENT MAJOR LABEL CHANGES

N/A

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

SUSVIMO (ranibizumab injection) is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD) who have confirmed response to and require frequent intravitreal injections (every 8 weeks or more frequently) of a Vascular Endothelial Growth Factor (VEGF) inhibitor medication in order to maintain visual acuity.

1.1 Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No notable difference in treatment effect and safety was seen with increasing age (see 4

Dosing Considerations**; Special Populations, Geriatrics** and 10.3 **Pharmacokinetics; Special Populations and Conditions, Geriatrics**).

2. CONTRAINDICATIONS

- Susvimo is contraindicated in patients who are hypersensitive to ranibizumab or any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.
- Susvimo is contraindicated in patients with active or suspected ocular or periocular infections.
- Susvimo is contraindicated in patients with active intraocular inflammation.

3. SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Endophthalmitis**
  Susvimo has been associated with a 3-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab. In clinical trials, 2.0% of patients receiving a ranibizumab implant experienced at least one endophthalmitis adverse event in the study eye. Many of these events were associated with conjunctival retractions or erosions (see 7 **WARNINGS AND PRECAUTIONS, Endophthalmitis** and 8.2 **Clinical Trial Adverse Reactions**). Endophthalmitis should be treated promptly to reduce the risk of vision loss. Appropriate conjunctiva management and early detection with surgical repair of conjunctival retractions or erosions may reduce the risk of endophthalmitis.
  - **Strict adherence to the manufacturer's most up-to-date Instructions for Use** for the Implant with Insertion Tool Assembly for Susvimo and Initial Fill Needle for Susvimo; Refill Needle for Susvimo; or Explant Tool for Implant for Susvimo **and training in implant procedures are required (**see 7 **WARNINGS AND PRECAUTIONS, Ophthalmologic,** 4.1 **Dosing Consideration,** 4.4 **Administration).**
  - **Susvimo should only be administered to patients who have been well informed of the risks associated with the Susvimo procedures of insertion, refill-exchange and removal.**

Patients should be instructed on how to take care of their eyes throughout treatment with Susvimo to prevent serious adverse events, including endophthalmitis. To receive Susvimo, patients should have also signed the surgical consent form as required by local clinical practice (see 4.4 **Administration).**

4. DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

General

- Susvimo is for intravitreal use via the implant for Susvimo only. Do not administer Susvimo by any other route (e.g., not as a bolus intravitreal injection).
- The implant initial fill and implant insertion, and implant removal procedures must be performed by an ophthalmologist experienced in vitreoretinal surgery and trained in implant procedures in an operating room using aseptic technique.
- The implant refill-exchange procedure should be performed under aseptic conditions by an ophthalmologist trained in the implant refill-exchange procedure.
- Read and refer to the manufacturer's most up-to-date Instructions for Use for the Implant with Insertion Tool Assembly for Susvimo and Initial Fill Needle for Susvimo; Refill Needle for Susvimo; or Explant Tool for Implant for Susvimo prior to initially filling, implanting, refilling or removing the implant.
- In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Susvimo.
- Do not substitute Susvimo for or with other formulations of ranibizumab.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of Susvimo is 2mg (0.02mL of 100 mg/mL solution) continuously delivered via the Susvimo implant with refills administered every 24 weeks (approximately 6 months).

Monitoring between the refill dosing visits may be required by the treating physician as needed.

Supplemental treatment with intravitreal ranibizumab injection

Supplemental treatment with 0.5 mg (10 mg/mL) intravitreal ranibizumab injection may be administered in the affected eye while the Susvimo implant is in place and if clinically necessary (see 14 **CLINICAL TRIALS**).

Please refer to the full prescribing information for 0.5 mg (10 mg/mL) intravitreal ranibizumab injection for supplemental treatment.

Dose (Refill-exchange) interruptions related to adverse events

For dose (refill-exchange) interruptions related to adverse events see **Table 1**.

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

Adverse Event	Modification
Intraocular inflammation ≥1+ cells or flare	Withhold dose (refill-exchange)

Adverse Event	Modification
Sight threatening adverse events (e.g. Rhegmatogenous retinal detachment, vitreous hemorrhage, unexplained vision loss, etc.)	Withhold dose (refill-exchange)
Local infections of either eye	Withhold dose (refill-exchange)
Infectious endophthalmitis	Withhold dose (refill-exchange)
Severe systemic infection	Withhold dose (refill-exchange)
Observed damage to the implant (e.g., septum dislodgement) or implant dislocation (see 7 **WARNINGS AND PRECAUTIONS**)	Withhold dose (refill-exchange) Consider implant removal Risks associated with removal or retention of a damaged or non-functional implant have not been established (see 7 **WARNINGS AND PRECAUTIONS, Others**). Refer to 4.4 **Administration, Susvimo Ocular Implant Removal**

Geriatrics (≥ 65 years of age)
No dose adjustment of Susvimo is required in patients ≥ 65 years of age (see 10.3 **Pharmacokinetics; Special Populations and Conditions, Geriatrics**).

Renal Impairment
See 10.3 **Pharmacokinetics; Special Populations and Conditions**.

Hepatic Impairment
The safety and efficacy of Susvimo have not been established in patients with hepatic impairment (see 10.3 **Pharmacokinetics; Special Populations and Conditions**).

4.3 Reconstitution
Not applicable.

4.4 Administration
- **Susvimo can only be administered** to patients who have been well informed of the risks associated with the Susvimo procedures of insertion, refill-exchange and removal and have signed the surgical consent form as required by local clinical practice.
- **Susvimo should only be administered** to patients who have been advised how to take care of their eyes to prevent serious adverse events, including endophthalmitis, throughout treatment with Susvimo, including after the insertion of implant surgery, refill-exchange, or removal of implant.
- Patients should be advised to **seek immediate care** from an ophthalmologist if there are sudden changes in vision throughout Susvimo treatment.

Susvimo Ocular Implant Initial Fill

The implant is initially filled with 0.02 mL of Susvimo (ranibizumab injection) prior to implant insertion. **No more than 30 minutes should pass between the initial fill of the ocular implant and the insertion into the patient's eye. The initial fill needle** should only be used for the initial fill.

Please refer to the manufacturer's most up-to-date Instructions for Use for the Initial Fill Needle for Susvimo.

Susvimo Ocular Implant Insertion
Susvimo ocular implant insertion is a surgical procedure that must be performed by an ophthalmologist experienced in vitreoretinal surgery and trained in Susvimo implant insertion procedures.

Please refer to the manufacturer's most up-to-date Instructions for Use for the Implant with Insertion Tool Assembly for Susvimo.

Susvimo Refill-Exchange
The Susvimo refill-exchange procedure must be performed under strict aseptic conditions by an ophthalmologist experienced in ophthalmic surgery and trained in Susvimo refill-exchange procedures. This includes the use of a surgical mask, sterile gloves, and a lid speculum.

The refill needle should only be used for the refill-exchange.

Please refer to the manufacturer's most up-to-date Instructions for Use for the Refill Needle for Susvimo.

Susvimo Ocular Implant Removal
Removal of the Susvimo ocular implant is a surgical procedure that must be performed with adequate anesthesia by an ophthalmologist experienced in vitreoretinal surgery and trained in Susvimo ocular implant removal procedures in an operating room under strict aseptic conditions. Implant removal can be performed at the physician's discretion should the benefit of the removal procedure outweigh the risk of the procedure and the risks of retaining a damaged or non-functional implant in the eye. **Please refer to the manufacturer's most up-to-date Instructions for Use for the Explant Tool for Implant for Susvimo.**

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

5. OVERDOSAGE

Based on the implant fill volume of 0.02 mL, the maximum amount of Susvimo that can be initially filled and subsequently refilled is approximately 2 mg.

For management of a suspected drug overdose, contact your regional poison control centre.

6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active

ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravitreal use with ocular implant.	Solution for injection 100 mg/mL	Histidine HCl, L Histidine, L Histidine Hydrochloride Monohydrate, Polysorbate 20, Sucrose, Water for Injection

Susvimo (ranibizumab) for intravitreal use via ocular implant for Susvimo is a clear to slightly opalescent, colourless to pale brown liquid supplied in a single-dose vial, containing 39.5 mg of ranibizumab in 0.395 mL of solution*. The implant is designed to contain approximately 0.02 mL (2 mg) of ranibizumab solution when filled.

*One mL solution contains 100 mg ranibizumab.

Two Susvimo pack types are available according to the procedure:

Initial fill kit

One glass vial of Susvimo and one initial fill needle [34G (0.18 mm) x 3 mm, 5 µm], for single use only.

Refill-exchange kit

One glass vial of Susvimo and one refill needle [34G (0.18 mm) x 5 mm, 5 µm], for single use only.

7. WARNINGS AND PRECAUTIONS

Please see 3 **SERIOUS WARNINGS AND PRECAUTIONS BOX**.

General

- Before deciding on whether to insert the implant that delivers ranibizumab, physicians should ensure that patients are fully aware of the risks associated with the implant and procedures, and are able to follow through appropriately on all eye care instructions provided, in order to prevent serious adverse events, including endophthalmitis. Patients should also be instructed to immediately report to their ophthalmologist any unexpected discomfort that might arise during the lifetime of the implant.
- In order to improve traceability of biological medicinal products and devices, the trade name and the batch/lot number of the product should be clearly recorded (or stated) in the patient file.
- The implant and/or implant-related procedures have been associated with endophthalmitis, rhegmatogenous retinal detachment, vitreous hemorrhage, conjunctival bleb, conjunctival erosion, conjunctival retraction, device (implant) dislocation, and septum dislodgement. Patients should be instructed to report signs or symptoms that could be associated with these events without delay. In some cases, these events can present asymptomatically. The implant and the tissue overlying the implant flange should be monitored carefully and routinely following the implant insertion and refill-exchange procedures to permit early medical or surgical intervention as necessary.

- Please refer to the manufacturer's most up-to-date Instructions for Use for the Implant with Insertion Tool Assembly for Susvimo and Initial Fill Needle for Susvimo; Refill Needle for Susvimo; or Explant Tool for Implant for Susvimo for additional WARNINGS AND PRECAUTIONS. Strict adherence to these manufacturer's most up-to-date Instructions and training in implant procedures is required to minimize procedure-related risks.
- The safety and efficacy of Susvimo in both eyes has not been studied. In clinical trials, patients with wet AMD in the fellow eye received anti-VEGF intravitreal injections.
- Risks associated with long-term use of Susvimo and its implant (including removal or retention of a damaged or non-functional implant, or replacement with a new implant) have not been established at this time.
- Special precautions need to be taken when handling Susvimo components (see 12 **SPECIAL HANDLING INSTRUCTIONS**).

Driving and Operating Machinery
Susvimo, implant, implant related-procedures and associated examinations have an influence on the ability to drive and use machines. Patients may experience temporarily reduced vision after implant-related procedures and the associated eye examination. Patients should not drive or use machines until the eye shield can be removed and visual function has recovered (see 8 **ADVERSE REACTIONS**).

Hypersensitivity
As with all therapeutic proteins, there is a theoretical risk of hypersensitivity reactions including anaphylaxis. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, severe anaphylactic/anaphylactoid reactions or severe intraocular inflammation. Patients should be instructed to report any symptoms of anaphylaxis, allergic reactions or intraocular inflammation (e.g., redness of the eye, eye pain, photophobia, etc.).

Ophthalmologic

- **Endophthalmitis**
  Susvimo has been associated with endophthalmitis (see 3 **SERIOUS WARNINGS AND PRECAUTIONS BOX**, 8.2 **Clinical Trial Adverse Reactions**). These events may result in severe vision loss/blindness. In the active comparator period of controlled clinical trials, Susvimo has been associated with a 3-fold higher rate of endophthalmitis adverse events than monthly intravitreal injections of ranibizumab (1.7% in the Susvimo arm vs 0.5% in the intravitreal arm). When including extension phases of clinical trials, 2.0% (11/555) of patients receiving the ranibizumab implant experienced an episode of endophthalmitis. Reports occurred between days 5 and 853, with a median of 173 days. Many of the cases of endophthalmitis reported a preceding or concurrent conjunctival retraction or erosion event.

  Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay. Endophthalmitis should be treated promptly and appropriately in an effort to reduce the risk of vision loss and maximize recovery. The Susvimo dose (refill-exchange) should be delayed until resolution of endophthalmitis (see 4.2 **Recommended Dose and Dosage Adjustment**).

  Patients should not have an active or suspected ocular or periocular infection or severe systemic infection at the time of any Susvimo implant or refill-exchange procedure. Strict aseptic technique should always be used during Susvimo implant insertion or refill-exchange procedures.

  Strict adherence to the manufacturer's most up-to-date Susvimo Instructions for Use is required (see 4.4 **Administration)**. Strict adherence to intraoperative handling, secure closure of the

conjunctiva and Tenon's capsule, and early detection and surgical repair of conjunctival erosions or retractions may reduce the risk of endophthalmitis.

- **Intraocular Inflammation**
  Intraocular inflammation has been reported in patients receiving Susvimo (see 8.2 **Clinical Trial Adverse Reactions**). These adverse events primarily occurred after the implant insertion surgery and during the post-operative period. In clinical trials in adult wet AMD patients, the most frequently reported type of intraocular inflammation in the study eye was iritis. The Susvimo dose (refill-exchange) should be delayed in the presence of Intraocular Inflammation > 1+ cells or flare (see 4.2 **Recommended Dose and Dosage Adjustment**).

  Appropriate sterility control before and during implant insertion surgery, and administration of post-operative eye medications should be used to minimize risk of intraocular inflammation.

- **Rhegmatogenous Retinal Detachment**
  Rhegmatogenous retinal detachment has been reported in patients receiving Susvimo and may result in severe vision loss (see 8 **ADVERSE REACTIONS**). Rhegmatogenous retinal detachment should be promptly treated with an intervention (e.g., pneumatic retinopexy, vitrectomy, or laser photocoagulation). The Susvimo dose (refill-exchange) should be delayed in the presence of retinal detachment or retinal break (see 4.2 **Recommended Dose and Dosage Adjustment**).

  Patients should be instructed to report any symptoms suggestive of rhegmatogenous retinal detachment without delay.

  Careful evaluation of the retinal periphery by scleral indentation should be performed, and any suspected areas of abnormal vitreo-retinal adhesion or retinal breaks should be treated before inserting the implant in the eye.

  Strict adherence to the manufacturer's most up-to-date Susvimo Instructions for Use (e.g. appropriate management of vitreous prolapse after pars plana incision) is required to minimize risks of rhegmatogenous retinal detachment (see 4.4 **Administration**).

- **Vitreous Hemorrhage**
  Vitreous hemorrhage has been reported in patients receiving Susvimo (see 8 **ADVERSE REACTIONS**). Vitreous hemorrhage may result in temporary vision loss. Vitrectomy may be needed in the case of a non-clearing vitreous hemorrhage. The Susvimo dose (refill-exchange) should be delayed in the event of sight-threatening vitreous hemorrhage (see 4.2 **Recommended Dose and Dosage Adjustment**).

  Patients on antithrombotic medication (e.g. oral anticoagulants, aspirin, nonsteroidal anti-inflammatory drugs) may be at increased risk of vitreous hemorrhage. Antithrombotic medications are recommended to be temporarily interrupted prior to the implant insertion procedure.

  Strict adherence to the manufacturer's most up-to-date Susvimo Instructions for Use (e.g. appropriate pars plana laser ablation, scleral cauterization) is required to minimize risks of vitreous hemorrhage (see 4.4 **Administration**).

- **Conjunctival Bleb**
  Conjunctival bleb has been reported in patients receiving Susvimo (see 8.2 **Clinical Trial Adverse Reactions**). A conjunctival bleb is an encapsulated elevation of the conjunctiva above the implant

flange, which may be secondary to subconjunctival thickening or fluid. Conjunctival blebs 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.

Strict adherence to the manufacturer's most up-to-date Susvimo Instructions for Use (e.g. appropriate scleral incision length, appropriate incorporation of conjunctiva and Tenon's capsule to preserve tissue integrity and secure peritomy closure, appropriate seating of the refill needle during refill-exchange procedure) is required to minimize risks of conjunctival blebs (see 4.4 **Administration**).

- **Conjunctival erosion or Conjunctival retraction**
  Conjunctival erosion and conjunctival retraction have been reported in patients receiving Susvimo (see 8.2 **Clinical Trial Adverse Reactions**). A conjunctival erosion is a full thickness degradation or breakdown of the conjunctiva in the area of the implant flange. A conjunctival retraction is a recession or opening of the limbal and/or radial peritomy. Conjunctival erosions or retraction 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 or retraction with or without exposure of the implant flange.

  Strict adherence to the manufacturer's most up-to-date Susvimo Instructions for Use (e.g. appropriate incorporation of conjunctiva and Tenon's capsule to preserve tissue integrity and peritomy closure, and appropriate placement of conjunctival sutures to avoid contact with the implant edge) is required to minimize risks of conjunctival erosion.

  Strict adherence to the manufacturer's most up-to-date Susvimo Instructions for Use (e.g. including appropriate suturing of the conjunctiva and Tenon's capsule to the limbus) is required to minimize risks of conjunctival retraction (see 4.4 **Administration**).

  The implant and the tissue overlying the implant flange should be monitored carefully and routinely following the implant insertion.

- **Traumatic Cataract**
  Traumatic cataract could potentially result from improper insertion of the implant's distal tip in close proximity to the patient's lens, excessive force applied during the refill-exchange resulting in eye indentation, dislocation of the implant into the vitreous cavity, or surgical removal of the dislocated implant. Perpendicular entry of the implant is important to avoid contact between the implant and intraocular structures such as the lens.

- **Intraocular Pressure Increased**
  Transient and sustained increases in intraocular pressure have been observed in clinical trials of Susvimo (see 8.2 **Clinical Trial Adverse Reactions**). Both intraocular pressure and perfusion of the optic nerve head must be monitored and managed appropriately.

  Susvimo has not been studied in patients with uncontrolled ocular hypertension or glaucoma (defined as intraocular pressure [IOP] > 25 mmHg or a cup to disc ratio > 0.8).

- **Postoperative Decrease in Visual Acuity**
  Visual acuity was decreased by 4 letters on average in the first postoperative month and 2 letters on average in the second postoperative month following initial implantation of Susvimo (see **Error! Reference source not found. CLINICAL TRIALS,** Error! Reference source not found.).

- **Device (implant) Dislocation**
  In clinical trials, the device (implant) has dislocated or subluxated into the vitreous cavity, or extend outside the vitreous cavity into or beyond the subconjunctival space (see 8.2 **Clinical Trial Adverse Reactions**). Device dislocation requires urgent surgical intervention. Consider removal of the device when the device is dislocated or is thought to be non-functional.

  Strict adherence to the manufacturer's most up-to-date Susvimo Instructions for Use (e.g. appropriate scleral incision length, appropriate targeting of the pars plana during laser ablation) is required to minimize risks of implant dislocation (see 4.4 **Administration**).

- **Septum Dislodgement**
  In clinical trials, a type of implant damage where the septum has dislodged into the body of the implant has been reported. Perform a dilated slit lamp exam and/or dilated indirect ophthalmoscopy 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 4.2 **Recommended Dose and Dosage Adjustment**).

  Strict adherence to the manufacturer's most up-to-date Susvimo Instructions for Use [e.g. appropriate handling and insertion of the refill needle into the septum (avoid twisting and/or rotation)] is required to minimize the risk of septum dislodgement (see 4.4 **Administration**).

- **Air Bubbles Causing Improper Filling of the Implant and Deflection of the Implant**
  Please refer to the manufacturer's most up-to-date Instructions for Use for the Implant with Insertion Tool Assembly for Susvimo.

Systemic Impact

- **Arterial thromboembolic events (ATEs) and Non-ocular hemorrahages**
  Systemic adverse events including arterial thromboembolic events (ATEs) and non-ocular hemorrhage have been reported following intravitreal delivery of VEGF inhibitors, including Susvimo (see 8 **ADVERSE REACTIONS**) and there is a theoretical risk that these may be related to VEGF inhibition. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, vascular death or death of unknown cause.

  There are limited data on safety of Susvimo in patients with history of stroke or transient ischemic attack or myocardial infarction.

Reproductive Health: Female and Male Potential

- **Contraception**
  Women of child bearing potential should use effective contraception while receiving Susvimo and for at least 12 months after the last dose (refill-exchange) of Susvimo.

- **Fertility**
  No studies on the effects of ranibizumab on fertility have been conducted (see 16 **NON-CLINICAL TOXICOLOGY**; Reproductive and Developmental Toxicology, Impairment of Fertility).

- **Reproduction**

  It is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with Susvimo may pose a risk to reproductive capacity (see 16 **NON-CLINICAL TOXICOLOGY**; Reproductive and Developmental Toxicology, Reproductive toxicity).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies of Susvimoin pregnant women.

A study in pregnant cynomologus monkeys given intravitreal ranibizumab throughout the period of organogenesis resulted in skeletal abnormalities (see 16 **NON-CLINICAL TOXICOLOGY**; Reproductive and Developmental Toxicology, Reproductive toxicity).

Due to its mechanism of action, Susvimo must be regarded as potentially teratogenic and embryo-/fetotoxic. Susvimo is not recommended during pregnancy unless the expected benefit outweighs the potential risk to the fetus. The implant may be flushed with saline using a refill needle should the patient become pregnant. For women who wish to become pregnant and have been treated with Susvimo, it is recommended to wait at least 3 months after the last dose of Susvimo before conceiving a child (See 17 **SUPPORTING PRODUCT MONOGRAPHS**).

Labor and Delivery

The safe use of Susvimo during labor and delivery has not been established.

7.1.2 Breast-feeding

It is not known whether ranibizumab is excreted in human breast milk after administration of Susvimo. No studies have been conducted to assess the impact of Susvimo on the breastfed infant or milk production or its presence in breast milk.

Because many drugs are excreted in human milk and the potential for absorption and harm to infant growth and development exists, as a precautionary measure, Susvimo is not recommended to nursing women.

7.1.3 Pediatrics

Pediatrics (< 18 years): Safety and efficacy in pediatric patients below the age of 18 have not been studied. Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

In the pivotal study, 90% (222 of 248) of the patients randomized to treatment with Susvimo were ≥65 years old, and approximately 57% (141 of 248) of patients were ≥75 years old. No notable difference in treatment effect and safety was seen with increasing age (see 4

Dosing Considerations; Special Populations, Geriatrics and Section 10.3 **Pharmacokinetics**; Special Populations and Conditions, Geriatrics).

8. ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The data provided below reflect adverse reactions of exposure of 248 patients with wet AMD in the Archway study to 2 mg of Susvimo delivered via the Susvimo implant following the Susvimo initial fill and implant insertion, refill, and implant removal procedures up to Week 40 unless otherwise specified. In patients treated with Susvimo:

- The adverse reactions that resulted in study discontinuation were endophthalmitis (0.8%), conjunctival retraction (0.4%), device dislocation (0.4%) and detachment of retinal pigment epithelium (0.4%).
- The most common (≥ 10%) adverse reactions were conjunctival hemorrhage (71.8%), conjunctival hyperemia (26.2%), iritis (20.6%), and eye pain (10.1%).
- The most common (≥ 2 patients [0.8%]) serious adverse reactions were endophthalmitis (1.6%), conjunctival retraction (0.8%), conjunctival erosion (0.8%), rhegmatogenous retinal detachment (0.8%), visual acuity reduced (0.8%).

The data provided below are of 248 patients in the Archway study as of the planned interim analysis after Week 40 with the clinical cut-off of Sept 11, 2020, at which point all enrolled patients had completed at least 60 weeks of follow-up or had discontinued the study early:

- There were 92%, 25%, 27% and 20% of patients who had experienced at least one ocular adverse event during 0-37 days after implantation, Day 38-Day 168, Day 169-Day 336 and Day 337-Day 504, respectively.
- There were 3.2%, 2.4%, 1.6% and 1.2% of patients who had experienced at least one ocular serious adverse event during 0-37 days after implantation, Day 38-Day 168, Day 169-Day 336 and Day 337-Day 504, respectively.

As of Sept 11, 2020, 18 patients (4.0%) underwent implant removal across all Susvimo studies (GR40548, GR40549, and GX28228). The reasons that resulted in implant removal were endophthalmitis (5 patients), device dislocation or damage (4 patients), lack of efficacy (4 patients), rhegmatogenous retinal detachment, conjunctival erosion, conjunctival retraction, wound secretion and drug hypersensitivity for one patient each.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 3 below lists adverse reactions, with causality, reported in the Archway study that occurred in greater than or equal to 1% of patients.

Table 3 Adverse Reactions occurring in ≥1% in the study eye in Study GR40548 (Archway) in wet AMD patients

Adverse Reactions Primary System Organ Class Preferred Term MedDRA Version: 23.0	Week 40	
	Susvimo (Ranibizumab 100 mg/mL) Q24W n = 248	Intravitreal ranibizumab 0.5 mg Q4W n = 167
Eye Disorders		
Conjunctival hemorrhage	72%	6%
Conjunctival hyperemia	26%	2%
Iritis[1]	23%	1%
Eye pain	10%	5%
Vitreous floaters	9%	2%
Conjunctival bleb/ filtering bleb leak[2]	9%	0
Foreign body sensation in eyes	7%	1%
Punctate keratitis	6%	2%
Hypotony of eye	6%	0
Vitreous detachment	6%	5%
Vitreous hemorrhage	5%	2%
Conjunctival edema	5%	0
Anterior chamber flare	4%	<1%
Corneal disorder	4%	0
Corneal abrasion[3]	4%	< 1%
Corneal edema	4%	0
Vision blurred	3%	3%
Ecchymosis	3%	0
Eye irritation	3%	< 1%
Eyelid ptosis	3%	0
Lacrimation increased	3%	0
Procedural pain	3%	0
Anterior chamber cell	2%	<1%
Blepharitis	2%	1%
Eye pruritus	2%	< 1%
Visual acuity reduced	2%	0
Conjunctival erosion	2%	0
Vitritis	2%	0

Adverse Reactions Primary System Organ Class Preferred Term MedDRA Version: 23.0	Week 40	
	Susvimo (Ranibizumab 100 mg/mL) Q24W n = 248	Intravitreal ranibizumab 0.5 mg Q4W n = 167
Conjunctival retraction	2%	0
Iris adhesions	2%	0
Ocular discomfort	2%	1%
Retinal hemorrhage	2%	< 1%
Conjunctivitis	2%	0
Endophthalmitis[4]	2%	0
Photophobia	2%	0
Intraocular pressure increased	2%	1%
Intraocular pressure decreased	2%	0
Iridocyclitis	1%	0
Injury, poisoning, procedural complications		
Headache[5]	7%	2%
Nausea[6]	2%	2%
Vomiting[7]	1%	< 1%

[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, subconjunctival cyst, and implant site cyst
[3] Corneal abrasion includes: corneal abrasion and vital dye staining cornea present
[4] In clinical studies, the management of endophthalmitis included a flush of implant contents with 100 µL (0.1 mL) of vancomycin (1 mg/0.1 mL), with or without previous flush with saline, in addition to standard of care.
[5] Headache includes: headache and procedural headache
[6] Nausea includes: nausea and procedural nausea
[7] Vomiting includes: vomiting and procedural vomiting

Description of selected adverse reactions

Endophthalmitis

In Study GR40548 (Archway), through Week 40, 1.6% (4/248) of patients receiving Susvimo reported 5 endophthalmitis events in the study eye. No patient in the monthly intravitreal ranibizumab arm reported an endophthalmitis event. All events were serious. When including the extension phases of all clinical trials, 2.0% (11/555) of patients receiving a ranibizumab implant experienced at least one endophthalmitis AE in the study eye. Six events were reported, preceding or concurrent with conjunctival erosion or retraction events. Seven events led to implant removal.

Intraocular Inflammation

In Study GR40548 (Archway), through Week 40, 19.4% (48/248) of patients receiving Susvimo experienced at least one intraocular inflammation event, according to the Standard Uveitis

Nomenclature classification within 7 days of surgery and 23% (57/248) of patients within the 37-day postoperative period. The most frequently reported category of intraocular inflammation in the study eye was iritis [16.5% (41/248) of patients within 7 days of surgery and 19.4% (48/248) of patients within the 37-day postoperative period]. The iritis events resolved with standard-of-care topical treatment. None of the iritis events were considered serious. Through Week 40, there were no iritis events in the intravitreal arm.

Rhegmatogenous retinal detachment
In Study GR40548 (Archway), through Week 40, 0.8% (2/248) of patients in the Susvimo arm experienced 3 rhegmatogenous retinal detachment events in the study eye. All rhegmatogenous retinal detachment events were severe and serious. No patients in the monthly intravitreal ranibizumab arm reported rhegmatogenous retinal detachment events. 0.9% (4/450) patients reported rhegmatogenous retinal detachment events across all ranibizumab implant studies.

Vitreous hemorrhage
In Study GR40548 (Archway), through Week 40, vitreous hemorrhages in the study eye were reported in 5.2% (13/248) of patients in the Susvimo arm and 2.4% (4/167) of patients in the monthly intravitreal ranibizumab arm. Based on a functional grading system, the majority of patients in the Susvimo arm (11/13) reported Grade 1 (< 15 letter BCVA loss from previous visit) and Grade 2 (16 – 30 letter BCVA loss from previous visit) events. In the monthly intravitreal ranibizumab arm, most patients (3/4 patients) reported Grade 1 events. In the Susvimo and monthly intravitreal ranibizumab arms, the majority of patients (12/13 and 3/4, respectively) experienced vitreous hemorrhage events that resolved spontaneously.

Conjunctival bleb/Conjunctival filtering bleb leak
In Study GR40548 (Archway), through Week 40, 8.5% (21/248) of patients in the Susvimo arm reported conjunctival bleb/conjunctival filtering bleb leak in the study eye and 5.6% (14/248) of patients reported these events in the post-operative period. The majority of Susvimo arm patients reported conjunctival bleb/conjunctival filtering bleb leak events that were mild (16/21) or moderate (4/21).

Conjunctival erosion
In Study GR40548 (Archway), through Week 40, 2.4% (6/248) of patients in the Susvimo arm reported conjunctival erosion in the study eye and 0.4% (1/248) of patients reported this event in the post-operative period. The majority of patients in the Susvimo arm reported conjunctival erosion events that were mild (4/6) or moderate (1/6). No patients in the monthly intravitreal ranibizumab arm reported conjunctival erosion events.

Conjunctival retraction
In Study GR40548 (Archway), through Week 40, 2% (5/248) of patients in the Susvimo arm reported conjunctival retraction in the study eye and 0.4% (1/248) of patients reported these events in the post-operative period. The majority of patients in the Susvimo arm reported conjunctival retraction events that were mild (1/5) or moderate (3/5). 1/5 patients had the implant removed as a result of conjunctival retraction. No patients in the monthly intravitreal ranibizumab arm reported conjunctival retraction events.

Device (implant) dislocation
In Study GR40548 (Archway), through Week 40, 0.4% (1/248) of patients receiving Susvimo reported device dislocation in the study eye. 1.1% (5/450) of patients receiving Susvimo reported device

dislocation in the study eye across all Susvimo studies. Events occurred between days 118 and 1113. All events were serious and 4 events led to implant removal. Eight (1.8%) patients reported device breakage, device failure, or a device deposit issue.

Septum dislodgement
Out of approximately 1,205 implants inserted and 4,121 refill exchange procedures conducted in patient eyes across all Susvimo clinical trials, septum dislodgement has been reported in approximately 1.6% (19) upon implant photo review by an independent image reading center or by the investigator.

8.3 Less Common Clinical Trial Adverse Reactions
Adverse reactions occurring in < 1% in Study GR40548 (Archway) and at a greater incidence in the Susvimo arm compared to the Intravitreal ranibizumab arm:

Eye Disorders: choroidal detachment, conjunctival disorder(may present as conjunctival thinning or thickening), eyelid edema, eye discharge, post procedural complication (reported as thickened tenons capsule over implant), post procedural discomfort, retinal tear, rhegmatogenous retinal detachment, scleral hyperemia, administration site discomfort (reported as refill site irritation - discomfort), device dislocation, device material opacification (reported as opacities of unknown etiology within implant) , foreign body in eye, hyphema, implant site fibrosis, implant site reaction (reported as exposed suture) , post procedural swelling, scleral thinning.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings
There were no findings to suggest a relationship between Susvimo and the development of clinically significant laboratory abnormalities.

Post-Market Adverse Reactions
Not applicable

9. DRUG INTERACTIONS

9.2 Drug Interactions Overview
No drug interaction studies have been performed.

9.3 Drug- Behavioral Interactions
No drug-behavioural interaction studies have been performed.

9.4 Drug-Drug Interactions
No drug-drug interaction studies have been performed.

9.5 Drug-Food Interactions
No drug-food interaction studies have been performed.

9.6 Drug-Herb Interactions
No drug-herb interaction studies have been performed.

9.7 Drug-Laboratory Test Interactions
No drug-laboratory interaction studies have been performed.

10. CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ranibizumab is a humanized 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 neovascularization, as well as vascular leakage, which contribute to the progression of the neovascular form of age-related macular degeneration.

10.2 Pharmacodynamics

Leakage of blood and fluid from choroidal neovascularization (CNV) may cause retinal thickening or edema and/or intraretinal/subretinal hemorrhage, resulting in vision loss.

In Archway, at week 36, the adjusted mean change in center point thickness (CPT) was 5.4 microns vs 2.6 microns in the Susvimo arm and intravitreal ranibizumab arm, respectively.

10.3 Pharmacokinetics

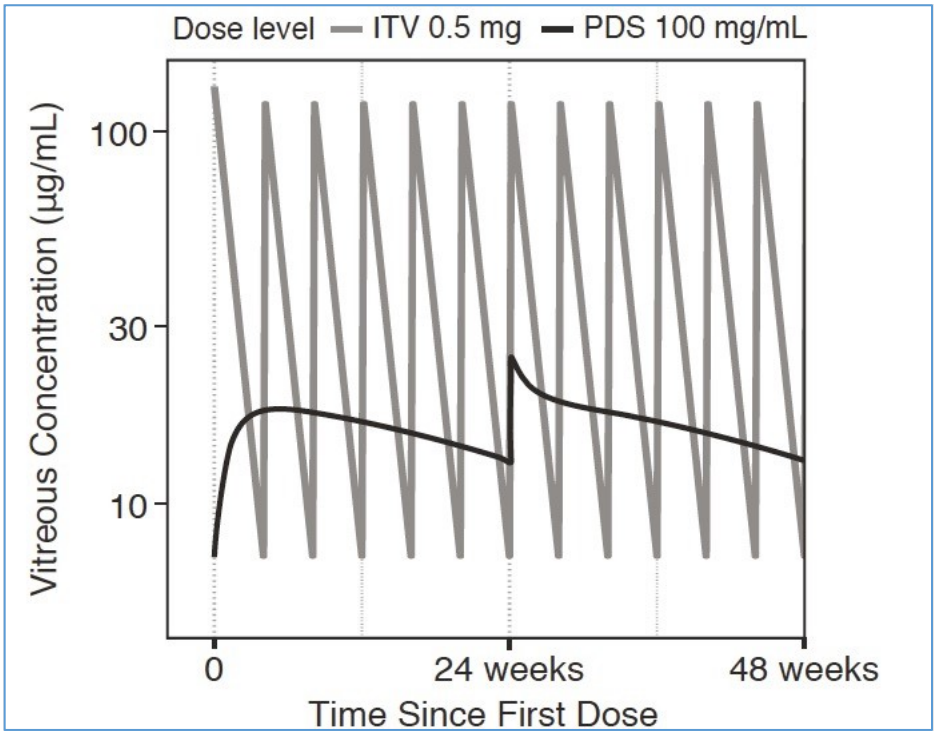
Vitreal and serum pharmacokinetics following treatment with Susvimo exhibit rate-limited elimination, driven by the release of ranibizumab from the implant.

Absorption

After insertion of implant, the release rate of ranibizumab into the vitreous decreases over time as the concentration gradient between the device and vitreous decreases. The vitreous concentrations decreased by half in 173 days after refill. The predicted vitreous concentrations with Susvimo are below the maximum and above the minimum concentrations experienced with monthly 0.5 mg intravitreal ranibizumab (see

Figure 1 below).

Figure 1 Predicted vitreous ranibizumab concentration versus time of Susvimo (ranibizumab) and monthly 0.5 mg intravitreal ranibizumab injection



PDS = Susvimo; ITV = intravitreal ranibizumab

Distribution

Following the initial fill and refill of Susvimo in patients with wet AMD, serum concentrations of ranibizumab were generally low, with maximum concentrations generally below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50%. Maximum serum concentrations, attained approximately 29 days after implantation and 7 days after refill, were observed ranging between 0.2 and 64.8 ng/mL, and minimum serum concentrations are predicted to be 0.25 ng/mL. Ranibizumab did not accumulate in serum when administered with refills every 24 weeks. Following ranibizumab administration via Susvimo or via intravitreal injection, serum ranibizumab exposure is predicted to be approximately 50,000-fold lower than vitreal ranibizumab exposure.

Metabolism

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

Elimination

Vitreal and serum pharmacokinetics following treatment with Susvimo exhibit rate-limited elimination, driven by the release of ranibizumab from the implant (see 10.3 **Pharmacokinetics**).

Special Populations and Conditions

- **Pediatrics**
  No studies have been conducted to investigate the pharmacokinetics of Susvimo in this population.

- **Geriatrics**
  Age did not have a significant effect on the pharmacokinetics of Susvimo (ranibizumab).

- **Hepatic Insufficiency**
  Hepatic Impairment
  No formal study has been conducted to examine the pharmacokinetics of Susvimo in patients with hepatic impairment.

- **Renal Insufficiency**
  Renal Impairment
  No formal study has been conducted to examine the pharmacokinetics of Susvimo in patients with renal impairment. In a population pharmacokinetic analysis of wet AMD patients with Susvimo, 75% (220 of 295) had renal impairment (42% mild [CrCL 60 to 89 mL/min], 30% moderate [CrCL 30 to 59 mL/min] and 2% severe [CrCL <30 mL/min]). The CL parameter in the model was slightly lower in renal impaired patients but was not clinically relevant.

11. STORAGE, STABILITY AND DISPOSAL

Store Susvimo vial at 2°C to 8°C 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.
Do not freeze. Do not shake.

This medicine should not be used after the expiry date (EXP) shown on the pack.

Keep out of reach and sight of children.

12. SPECIAL HANDLING INSTRUCTIONS

- Refer to the manufacturer's most up-to-date Instructions for Use for the Implant with Insertion Tool Assembly for Susvimo and Initial Fill Needle for Susvimo; Refill Needle for Susvimo or Explant Tool for Implant for Susvimo for use for a complete list of indications, contraindications, warnings, precautions, adverse events, and instructions for use of the device.
- Strict aseptic procedures must be used during the preparation and handling of the Susvimo vial and when filling and refilling the implant.
- Susvimo vials should be inspected visually for particulate matter and discolouration prior to administration. Susvimo is a clear to slightly opalescent, colourless to pale brown liquid. Do not use Susvimo if the medicine has particulate matter, cloudiness or discolouration.
- The contents of the vial and the initial fill and refill needles are supplied sterile and are for single use only. Do not reprocess, resterilize, or reuse any component. Do not use any component if it is damaged, broken, or the sterility has been compromised.

Incompatibilities
No incompatibilities between Susvimo and polyacrylic, polyamide, polypropylene, polycarbonate, or polyethylene have been observed.

Susvimo should not be mixed or diluted with other drugs.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

The following point should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- All used needles and syringes must be placed into a sharps container (puncture-proof disposable container).
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13. PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: ranibizumab

Chemical name: immunoglobulin G1, anti-human VEGF Fab fragment (human-mouse monoclonal rhuFab V2 G1-chain), disulfide with human-mouse monoclonal rhuFab V2 k-chain

Molecular formula and molecular mass: Approximately 48,379 Da (peptide chains only)

Structural formula: Ranibizumab is the antigen binding fragment (Fab) of a humanized monoclonal antibody based on a human IgG1 framework containing heavy chain V_HIII and light chain V_L κI subgroup sequences. The recombinant antibody fragment is produced in *E. coli* and consists of one heavy chain (231 amino acid residues) and one light chain (214 amino acid residues).

Amino Acid Sequence of Ranibizumab Light Chain

```
         10        20        30        40        50        60
DIQLTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPS
         70        80        90       100       110       120
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPP
        130       140       150       160       170       180
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
        190       200       210
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
```

Note 1: The calculated molecular mass of the light chain is 23,433 Da (cysteine residues are in the reduced form).

Note 2: Complementarity-determining regions are underlined.

Amino Acid Sequence of Ranibizumab Heavy Chain

```
          10        20        30        40        50        60
EVQLVESGGGLVQPGGSLRLSCAASGYDFTHYGMNWVRQAPGKGLEWVGWINTYTGEPTY
          70        80        90        100       110       120
AADFKRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPYYYGTSHWYFDVWGQGTLVT
         130       140       150       160       170       180
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
         190       200       210       220       230
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHL
```

Note 1: The calculated molecular mass of the heavy chain is 24,957 Da (cysteine residues are in the reduced form).

Note 2: Complementarity determining regions are underlined.

Physicochemical properties: Ranibizumab is a clear to slightly opalescent, colourless to pale brown liquid. The pH of the ranibizumab liquid is in the range of 5.2 - 5.8.

Pharmaceutical standard: Professed

Product Characteristics:
Ranibizumab is a humanized recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It is produced in *Escherichia coli* expression vector by standard recombinant DNA technology.

14. CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of Wet AMD
The clinical efficacy and safety of Susvimo were assessed in a randomized, visual assessor-masked, open-label active treatment-controlled Study GR40548 (ARCHWAY) in patients with wet AMD. A total of 415 patients (248 in the Susvimo arm and 167 in the intravitreal ranibizumab arm) were enrolled and treated in this study.

Table 4 Summary of trial design and patient demographics for clinical trials in wet AMD

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
GR40548 (ARCHWAY)	randomized, multicenter, open-label (visual assessor masked), active-controlled study	Susvimo: 100 mg/mL Q24W Intravitreal ranibizumab 0.5 mg Q4W	Susvimo n=248 Intravitreal ranibizumab n = 167	75.0 years (65-85 years)	Male: 41.0 % Females: 59.0 %

Patients were diagnosed with any type of macular choroidal neovascularization (CNV) related to wet AMD 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. They have demonstrated a response to anti-VEGF intravitreal agents defined as overall decrease in wet AMD disease activity detected on spectral-domain optical coherence tomography (SD-OCT) and stable or improved vision.

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.

Patients were randomized in a 3:2 ratio to receive continuous delivery of Susvimo via the implant every 24 weeks or 0.5 mg intravitreal ranibizumab injections every 4 weeks. For patients randomized to the Susvimo arm, supplemental treatment with intravitreal injections of 0.5 mg ranibizumab was available at Weeks 16, 20, 40, 44, 64, 68, 88, and 92, if one of the following criteria was met: a loss of 15 letters from the best recorded Best Corrected Visual Acuity (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.

Prior to study treatment, a median of 4 doses of anti-VEGF intravitreal agents were administered in the study eye of patients in the Susvimo and intravitreal ranibizumab arms. The mean change in visual acuity in the study eye from diagnosis of wet AMD to baseline was 11.3 ETDRS letters. Approximately 75% of Susvimo patients (who were not treatment naive) were treated with a monthly intravitreal regimen per standard of care before enrollment in the study, while 25% of patients were treated with intravitreal regimens ranging from every 6 weeks to every 12 weeks.

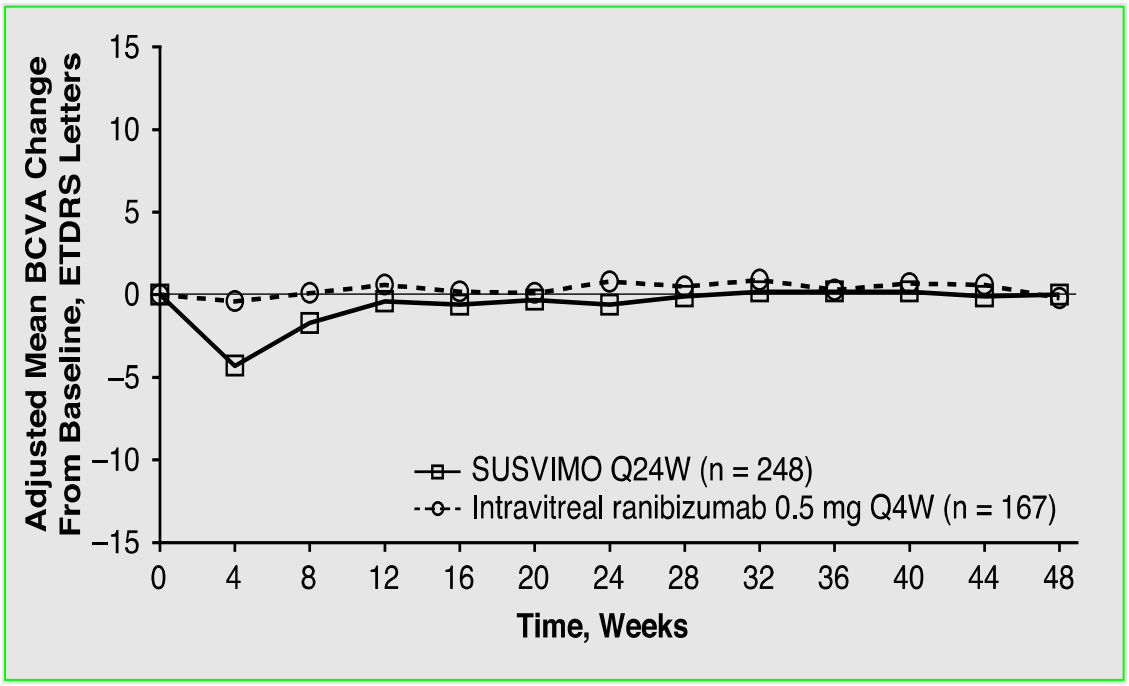
The primary efficacy endpoint of change from baseline in BCVA score averaged over Week 36 and Week 40 demonstrated Susvimo to be equivalent to intravitreal ranibizumab injections administered every 4 weeks. Detailed efficacy results are shown in **Table 5** and **Figure 2** below.

Table 5 Visual acuity outcomes at Week 40 in Study GR40548 (ARCHWAY)

Outcome Measure*	Susvimo 100mg/mL n=248	Intravitreal ranibizumab 0.5 mg (10mg/mL) n=167	Difference (95% CI)**
Mean BCVA letter score at baseline	74.4	75.5	
Adjusted Mean change from baseline in BCVA score averaged over Weeks 36 and 40	0.2	0.5	-0.3 (-1.7, 1.1)***

BCVA = Best corrected visual acuity
* BCVA measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters score
**All estimates are adjusted estimates based on a mixed-effect model with repeated measures for mean change from baseline or based on Cochran-Mantel-Haenszel weighting for proportion of patients. Susvimo arm –intravitreal ranibizumab arm. The type 1 error was adjusted for interim safety monitoring.
*** Equivalence margins were ±4.5 letters.

Figure 2 Adjusted Mean Change from Baseline in Best Corrected Visual Acuity in Study Eye through Week 48 in the Study GR40548 (ARCHWAY) study*



PDS with ranibizumab = Susvimo arm; Q24W = every 24 weeks; Q4W = every 4 weeks
* Decrease in BCVA at Week 4 during post-operative recovery period.

In the first 24 week treatment period, 1.6% of patients in the Susvimo arm received 1 or more supplemental treatment with 0.5 mg intravitreal ranibizumab injections. In the following 24 week treatment period, 5.4% of patients received 1 or more supplemental treatment.

14.3 Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response to ranibizumab.

In previously treated wet AMD patients in the Archway study, anti-ranibizumab antibodies were detected in 2.1% (5 of 243) of patients prior to insertion of the implant. After implant insertion and treatment, anti-ranibizumab antibodies developed in 11.7% (29 of 247) patients.

No clinically meaningful differences in the pharmacokinetics, efficacy, or safety in patients with treatment-emergent anti-ranibizumab antibodies were observed.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to Susvimo with the incidence of antibodies to other products may be misleading.

15. MICROBIOLOGY

No microbiological information is required for this drug product.

16. NON-CLINICAL TOXICOLOGY

Carcinogenicity

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

Genotoxicity

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

Reproductive and Developmental Toxicology

- **Impairment of Fertility**
  No fertility studies in animals have been performed to evaluate the effect of ranibizumab delivered via the implant.

  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 ranibizumab delivered via the implant.

Intravitreal ranibizumab injection

An embryo-fetal developmental toxicity study with intravitreal ranibizumab was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal ranibizumab injections every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. The intravitreal ranibizumab injection doses of 0.125 and 1.0 mg/eye administered in a 50 µL volume, give maximum maternal serum levels (C_{max}) of 30- and 300- fold, respectively, higher than the median C_{max} in humans given monthly unilateral Susvimo 100 mg/mL. See 17 **SUPPORTING PRODUCT MONOGRAPHS**. 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 1 mg/eye of ranibizumab.

No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough concentrations equivalent to single eye treatment with Susvimo in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed. The systemic exposure to Susvimo is low after administration via the implant, but due to its mechanism of action, Susvimo must be regarded as potentially teratogenic and embryo-/fetotoxic. Therefore, Susvimo is not recommended during pregnancy unless the expected benefit outweighs the potential risk to the fetus (see 7 **WARNINGS AND PRECAUTIONS**; Reproductive Health: Female and Male Potential and 7.1.1 **Pregnant Women**).

17. SUPPORTING PRODUCT MONOGRAPHS

i. PrLUCENTIS® (ranibizumab injection) Product Monograph, Submission Control No: 245596 dated December 21, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] SUSVIMO™

ranibizumab injection, solution for intravitreal use via SUSVIMO ocular implant

Read this carefully before you start taking **Susvimo** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and if there is any new information about **Susvimo**.

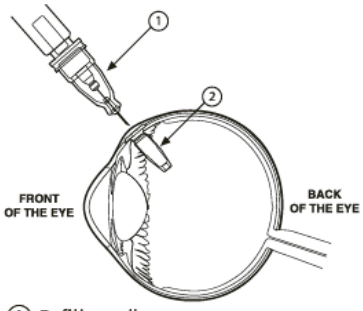
Serious Warnings and Precautions

- **Endophthalmitis:** The Susvimo implant could cause endophthalmitis (an infection of the eyeball that can cause blindness and permanent damage to your eye). The chance to have endophthalmitis associated with Susvimo is 3-times greater than monthly intravitreal injection of anti- vascular endothelial growth factor agent in the eye. Endophthalmitis requires **urgent (same day)** medical or surgical treatment. **Call your healthcare provider right away and seek immediate care** from an ophthalmologist if you have increasing eye pain, vision loss, sensitivity to light, or redness in the white of the eye.
- You can only receive Susvimo if you have been well informed of the risks associated with Susvimo, procedures of insertion, refill-exchange and removal, and ocular implant dislocation, and have been well instructed on how to take care of your eye to prevent serious side effects including endophthalmitis throughout treatment with Susvimo and have signed the surgical consent form provided by your doctor.

What is Susvimo used for?
SUSVIMO (ranibizumab) is used to treat adults with neovascular (wet) age-related macular degeneration (AMD) who have previously responded to and need frequent treatment (every 8 weeks or more frequently) with a Vascular Endothelial Growth Factor (VEGF) inhibitor medication in the gel-like part of the eye (intravitreal) in order to maintain vision gain. This condition is caused by small, abnormal blood vessels that grow in the back of the eye (retina). The abnormal vessels may leak blood or fluid in the macula (center part of the retina). This can lead to scars that may make your vision worse and lead to blind spots.

How does Susvimo work?
A protein called vascular endothelial growth factor (VEGF) helps to form the leaky blood vessels in the back of the eye (macula). Susvimo is a medicine that contains the ingredient ranibizumab. It attaches to and blocks VEGF protein. This stops or slows the growth and leakage from the abnormal blood vessels in your eye.

Susvimo is made to be released through an implant that stays in your eye. A doctor will perform surgery to place the implant in your eye. It is about the size of a grain of rice. It will need to be refilled with the medicine Susvimo which can be done through an injection. The picture (Figure 1) below shows how the implant will be refilled with the medicine using a refill needle and where the implant can be found in the eye.



① Refill needle
② Implant for Susvimo (ranibizumab)

Figure 1

What are the ingredients in Susvimo?
Medicinal ingredients: ranibizumab. One mL of solution contains 100 mg of ranibizumab.

Non-medicinal ingredients: Histidine HCl, L Histidine, L Histidine Hydrochloride Monohydrate, Polysorbate 20, Sucrose, Water for Injection

Susvimo comes in the following dosage forms:
Solution for Injection (100 mg/mL)

Susvimo is the medicine that gets injected into the ocular implant. Susvimo is in a vial and is a clear to slightly opalescent, colourless to pale brown liquid.

Two pack types are available:

Initial fill kit (to fill your implant the first time)
One vial of Susvimo and 1 initial fill needle [34G (0.18 mm) x 3 mm, 5 µm]

Refill-exchange kit (to refill your implant)
One vial of Susvimo and 1 refill needle [34G (0.18 mm) x 5 mm, 5 µm]

Do not use Susvimo if:

- You are allergic to ranibizumab or any of the other ingredients in Susvimo or any component of the container (see list of ingredients provided above). If you think you may be allergic, ask your doctor for advice.
- You have, or think you have, an infection in or around your eye.
- You have inflammation in your eye (you may feel pain or have redness in your eye or have swelling around your eye).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Susvimo. Talk about any health conditions or problems you may have, including if you:

- **Develop endophthalmitis** (an infection of the eyeball that can cause blindness and permanent damage to your eye) **or severe inflammation of your eye**. This requires **urgent (same day)**

medical or surgical treatment. **Call your healthcare provider right away if you have increasing eye pain, vision loss, sensitivity to light, or redness in the white of the eye**.

- **Develop rhegmatogenous retinal detachment** (tear and separation of layers of the retina in the back of the eye that senses light). Rhegmatogenous retinal detachment can cause blindness and requires **urgent** surgical treatment. **Call your healthcare provider or go to the emergency room right away if you see flashing lights, see a curtain or veil covering part of your vision, have a change in your vision, or a loss of vision**.
- **Develop vitreous hemorrhage** (bleeding within the gel-like substance [vitreous] inside of your eye)**: Call your healthcare provider right away if you have an increase in moving spots or what looks like spider webs in your vision.** You may need surgical treatment.
- **Develop conjunctival erosion** (a missing layer on top of the white part of the eye). It could result in exposure of the implant. Conjunctival erosion may require surgical treatment.
- **Develop conjunctival bleb** (a small bulge in the layer that covers the white part of the eye where the implant was placed)**, have a sudden feeling that something is in your eye** (foreign body sensation)**, have eye discharge, or watering of the eye.** Conjunctival bleb may require surgical treatment.
- **Develop conjunctival retraction** (an opening of the layer that covers the white part of the eye)**.** Conjunctival retraction may cause the implant to be exposed and may require surgical treatment. **Call your healthcare provider right away if you suddenly feel that something is in your eye, or have eye discharge, or watering of the eye.**
- **Notice that the implant has moved out of place (device dislocation).** This movement may require **urgent** surgical treatment to correct. **Tell your healthcare provider right away if you notice that the implant has moved out of place**.
- **Notice damage to the implant [that prevents continued treatment (refills) with Susvimo].** If this damage prevents proper filling of the implant, your wet AMD may be inadequately treated and your physician may remove the implant from your eye and/or change your treatment.
- **Develop signs of a possible allergic reaction** (for example, fast pulse, low blood pressure, sweating, allergic skin reactions such as rash, itching or stinging).
- **The use of** Susvimo **may cause temporary decrease in vision after the Susvimo insertion procedure.**
- **Susvimo may cause an increase in eye pressure.** Your healthcare provider will check your eye pressure.
- **Susvimo may cause cataract** (clouding of the eye lens).
- **The use of Susvimo is potentially related to the risk of blood clots blocking blood vessels** (arterial thromboembolic events). This may lead to heart attack or stroke.

Other warnings you should know about:

- There is no experience of using Susvimo in both eyes.

Contraception: Women who could become pregnant must use effective contraception (birth control) during treatment and for at least 12 months after the last refill with Susvimo.

Pregnancy: There is no experience of using Susvimo in pregnant women. However, based on how Susvimo works, it could harm your unborn baby. Susvimo should not be used during pregnancy unless the benefit of the medicine is greater than the risk to your unborn baby.

If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine.

If you become pregnant while taking this medicine, your doctor may replace Susvimo from the implant with salt water solution (saline).

Breastfeeding: Susvimo is not recommended during breast-feeding because it is not known whether the medicine will pass into human milk. Ask your doctor or pharmacist for advice before Susvimo treatment.

Children and adolescents (below 18 years of age): Susvimo is NOT used in children and adolescents. The use of Susvimo has not been studied in children and adolescents.

Ability to drive and use machines: You may have decreased vision for a short period of time when you:

- first get your implant placed in your eye
- if you have the implant removed
- receive a refill of Susvimo
- because of some of the tests that are done to your eye during your appointment

Do not drive or use machines until you can remove the eye shield (as advised by your doctor) and your vision has gotten better.

Use with Standard Procedures:
If you are prescribed:

- an ultrasound for your eye (A-scan ophthalmic ultrasound)
- slit lamp examination (using a microscope with a bright light during your eye exam)
- indirect ophthalmoscopy (an exam of the inside of the back of the eye using a beam of light and a handheld lens)
- tonometry (a test to measure the pressure inside your eye), a scan that uses light beams to make detailed pictures of the inside of your eye (optical coherence tomography-OCT)
- a test to see how much you can see out of the corner of your eye (visual field or perimetry)
- laser treatments that may be used by your eye doctor
- radiography (x-ray)
- computed tomography (CT) scan
- fluorescein/indocyanine angiography (an eye test that uses a special dye and camera to look at blood flow in certain parts of the eye)
- fundus autofluorescence (a test that creates a picture from colours in the back of your eye that give out light).

Inform your clinician that you have an implanted medical device.

Important Note on Magnetic Resonance Imaging (MRI):
Get your implant card from your healthcare provider after receiving the ocular implant and keep the card in a safe place for future reference. If you need to undergo an MRI, let your doctor know that you have an implant in your eye and show the healthcare provider your Susvimo implant card. This is

especially important as you may only have an MRI under specific scan conditions which your healthcare provider can confirm.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

- Especially if you are taking medicines that reduce the formation of blood clots (such as warfarin, low or regular doses of aspirin, or nonsteroidal anti-inflammatory drugs (e.g. ibuprofen, naproxen).

How to take Susvimo:

- **You can only receive Susvimo if you** have been fully informed the risks associated with Susvimo, procedures of insertion, refill-exchange and removal, ocular implant dislocation and damage, and have signed the surgical consent form provided by your doctor.
- **You can only receive Susvimo if you** have been fully instructed how to take care of your eye throughout treatment with Susvimo, including after the surgery to insert the implant, after refill and after implant removal if needed.
- Before receiving Susvimo your doctor will check that you respond to this kind of medicine. **You can only receive Susvimo if you** have responded to previous injections of a Vascular Endothelial Growth Factor (VEGF) inhibitor in the gel-like part of the eye (intravitreal) and require intravitreal injections of an anti-VEGF medication every 8 weeks or more frequently in order to maintain vision gain.
- Susvimo will be given to you by a healthcare professional in a healthcare setting.
- An eye surgeon trained to put in implants will fill the implant with Susvimo before placing it in your eye.
- An eye surgeon trained in implant insertion procedures will insert the implant in your eye.
- Afterwards, your eye doctor trained in refill procedures will refill the implant every 6 months.
- Your doctor(s) will perform both of these procedures using a local anesthetic to numb the eye and will be careful to lower the risk of infection by using sterile procedures (procedures that are very clean).

Susvimo must only be given using the implant.

Monitoring and care during your treatment with Susvimo:

Your doctor will monitor your condition and that of the implant throughout your treatment with Susvimo to allow for prompt medical assistance if necessary (see "**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Susvimo. Talk about any health conditions or problems you may have, including if you:**" and "**Other warnings you should know about"**)**.** Follow you doctor's instructions for how to care for the treated eye. These instructions include but are not limited to the following:

After the surgery to insert the implant:

Positioning of your head

- Keep your head above shoulder level for the rest of the day.
- Sleep with your head raised up on 3 or more pillows if lying down during the day and night after the implant is put in.

How to care for your eye

- **Do not** remove the eye shield from the eye until you are told to by your doctor. At bedtime, keep wearing an eye shield for **at least 7 nights** after the implant has been placed.
- Take all eye medications after surgery, as directed by your doctor.
- **Do not** push on the eye, rub the eye, or touch the area of the eye where the implant is placed (i.e. underneath the eyelid in the upper and outer part of your eye) **for 30 days** after the implant has been placed.
- **Do not** take part in any strenuous activities until **1 month** after the implant has been placed or after talking with your doctor.

See Important Note on Magnetic Resonance Imaging (MRI) on page 32.

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 (i.e. underneath the eyelid in the upper and outer part of your eye) for **7 days** after the refill procedure.
- Put antimicrobial (kills different germs such as bacteria or viruses) eye drops into the eye, as directed by your doctor.

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

- Keep your head above shoulder level for the rest of the day.
- Sleep with your head raised up on 3 or more pillows if lying down during the day and night after the implant has been taken out.
- Wear an eye shield for **at least 7 nights** following the implant removal procedure.
- Do not participate in strenuous activities until **14 days** following the implant removal procedure.
- Administer all post-operative anti-inflammatory and antimicrobial drops, as directed by your doctor.

Throughout treatment with Susvimo:

- Upon receiving the ocular implant, do not drive or use machinery until the eye shield can be removed as directed by your doctor and visual function has recovered sufficiently (see "**Ability to drive and use machines**").
- **Avoid** rubbing your eye or touching the area of your eye where the implant is placed as much as possible (this area is shown as 2 in the Figure 1 under "**How does Susvimo work?**"). If you have to rub or touch your eye, make sure your hands are cleaned before touching the eye.
- Susvimo, implant and/or implant related procedures have been associated with endophthalmitis or severe inflammation of the eye, rhegmatogenous retinal detachment, conjunctival reactions (bleb, erosion, retraction), vitreous hemorrhage, the dislocation of the implant, septum dislodgement, a temporary decrease in vision, an increase in eye pressure or development of a cataract (see "**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Susvimo. Talk about any health conditions or problems you may have, including if you:**"
- **Seek immediate care from an ophthalmologist if there are sudden changes in vision** (an increase in moving spots, the appearance of "spider webs", flashing lights, or a loss in vision), increasing eye pain, progressive vision loss, sensitivity to light, redness in the white of the eye, a sudden sensation that something is in their eye, or eye discharge or watering. **Immediately** report any signs and symptoms of reactions that may need urgent medical or surgical treatment and/or a delay in your next refill of Susvimo as long as the implant is in place (see

"**Serious side effects and what to do about them**" and "**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Susvimo. Talk about any health conditions or problems you may have, including if you:**").

Usual dose:
The recommended dose of Susvimo is 2 mg and it will be continuously delivered by the implant. The implant is refilled every 24 weeks (approximately 6 months) by your doctor.

Depending on how you respond to treatment with Susvimo, your doctor may give you additional injection(s) into your eye (intravitreal injections) of a different form of ranibizumab within the 24-week refill interval.

Your doctor will regularly monitor your condition to check that the treatment is working for you.

While monitoring your condition, your doctor may feel it necessary to stop the refills of Susvimo or safely remove the implant through surgery.

Overdose:

If you think you, or a person you are caring for, have administered too much Susvimo, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose (scheduled refill), schedule a new appointment with your doctor to receive the refill as soon as possible. Do not wait until the next planned refill.

What are possible side effects from using Susvimo?
These are not all the possible side effects you may have when taking Susvimo. If you experience any side effects not listed here, tell your healthcare professional.

The list of possible side effects from treatment with Susvimo include side effects related to Susvimo (the medication in the implant), the presence of the implant in the eye, and the procedures to place the implant in the eye, refill the implant, and remove the implant.

Tell your doctor if experience any of the following side effects:

Very common: may affect more than 1 in 10 people
- blood on top of the white of the eye (conjunctival hemorrhage)
- swelling of the coloured part of the eye (iritis)
- eye pain

Common: may affect up to 1 in 10 people
- moving spots in your vision (vitreous floaters)
- feeling like that something might be in the eye(s) (foreign body sensation in eyes)
- bleeding within the gel-like substance at the back of the eye (vitreous hemorrhage)
- low pressure inside the eye (hypotony of 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)
- pain during the procedure
- inflammation of the eyelid (redness, pain, swelling, and itching of the eyelids, eyelid scales) [blepharitis]
- eye irritation (burning, stinging, itching, tearing, redness)
- swelling of the layer that covers the white part of the eye (conjunctival edema)
- bleeding from the blood vessels in the back of the eye (retinal hemorrhage)
- swelling of the clear part at the front of the eye (corneal edema)
- blurred vision
- scratch to the clear part at the front of the eye (corneal abrasion)
- problem with the clear part (cornea) at the front of the eye (corneal disorder)
- drooping of the upper eyelid (eyelid ptosis)
- less sharpness of vision (visual acuity reduced)
- itchy eyes (eye pruritis)
- more tears than usual/watering eyes (lacrimation increased)
- infection of the layer that covers the white of the eye (conjunctivitis)
- problem in the layer that covers the white part of the eye (conjunctival disorder)
- bruising around the eye following surgery (ecchymosis)
- swelling of the eyelid (eyelid edema)
- attachment of the coloured part of the eye (iris) to other structures in the eye (iris adhesions)
- eye discomfort (ocular discomfort)
- less pressure of the eye (intraocular pressure decreased)
- eyes are more sensitive to light (photophobia)
- inflammation of the gel-like substance at the back of the eye (vitritis)
- leaking fluid from your eye (eye discharge)
- blood in front of the coloured part (iris) of the eye (hyphema)
- inflammation of the iris (coloured part of the eye) and its nearby tissue in the eye (iridocyclitis)
- headache
- nausea
- vomiting
- damage to the implant

Uncommon: may affect up to 1 in 100 people
- separation of the layer of blood vessels (called the choroid) from underneath the white part of the eye (choroidal detachment)
- redness in the white part of the eye (scleral hyperemia)
- separation of the layer (retina) in the back of the eye that senses light (rhegmatogenous retinal detachment)
- thinning of the white part of the eye (scleral thinning)
- discomfort after a refill at or around the area where Susvimo implant was placed (administration site discomfort)
- problems that may happen after the procedure to place the Susvimo implant in your eye (e.g. a stitch can be seen)
- discomfort after the procedure (post procedural discomfort)
- hole or tear in layer (retina) in the back of the eye that senses light (retinal tear)

- cloudiness of the Susvimo implant (device material opacification)
- scar tissue at the place where the Susvimo implant was inserted (implant site fibrosis)
- a reaction (e.g. swelling) at or around the place where Susvimo implant was placed (implant site reaction)
- swelling after the procedure

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Redness in the layer that covers the white of the eye (conjunctival hyperemia)		✓	✓
COMMON			
Infection of the eyeball with inflammation of the inside of the eye or increasing eye pain, vision loss, sensitivity to light, or redness in the white of the eye (endophthalmitis)		✓	✓
See flashing lights, see a curtain or veil covering part of your vision, have a change in your vision, or a loss of vision (rhegmatogenous retinal detachment)		✓	✓
Experience sudden changes in your vision (moving spots in your vision, the appearance of “spider webs”, flashing lights, a change in your vision, or a loss in vision) (vitreous hemorrhage)		✓	✓
Sudden feeling that something is in your eye(s)		✓	✓
Eye discharge or watering		✓	✓
Gap in the layer that covers the white of the eye near the cut where the implant was placed (this may cause the implant to become uncovered) (conjunctival retraction)		✓	✓
Leakage of fluid from blister-like bulge in the layer that covers the white part of the eye (conjunctival filtering bleb leak)		✓	✓
Wearing away of the layer that covers the white part of the eye (may cause exposure of the implant) [Conjunctival erosion]		✓	✓
Cataract (clouded, blurred or dim vision)		✓	
Implant moves out of place (device dislocation)		✓	✓
Implant damage		✓	✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Allergic reactions (fast pulse, low blood pressure, sweating, allergic skin reactions such as rash, itching or stinging)		✓	✓
Signs of stroke (weakness or paralysis of limbs or face, difficulty speaking or understanding, sudden blurring or loss of vision)		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep this medicine out of the sight and reach of children. Store Susvimo and the Initial fill and Refill-exchange kits in the refrigerator at 2°C to 8°C in the original carton to protect from light. Prior to use, the unopened vial may be kept at 9°C to 30°C for up to 24 hours. Do not freeze. Do not shake.

If you want more information about Susvimo:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.rochecanada.com), or by calling 1-888-762-4388.

This leaflet was prepared by Hoffmann-La Roche Limited.

Last Revised: SEPT 14, 2022

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