Date: 23 June 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

VABYSMO

International non-proprietary name: faricimab
Pharmaceutical form: solution for injection for intravitreal use
Dosage strength(s): 120 mg / mL
Route(s) of administration: intravitreal
Marketing Authorisation Holder: Roche Pharma (Schweiz) AG
Marketing Authorisation No.: 68395
Decision and Decision date: approved on 25 May 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
Ang-2	Angiopoietin-2
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DME	Diabetic macular oedema
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
nAMD	Neovascular (wet) age-related macular degeneration
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
VEGF	Vascular endothelial growth factor

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance faricimab of the medicinal product mentioned above.

Work-sharing procedure
The applicant requested a work-sharing procedure with Switzerland, Canada, Australia, Singapore and the United Kingdom.
The Access NAS (New Active Substance) work-sharing initiative is a collaboration between regulatory authorities, i.e. Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), Swissmedic, and the pharmaceutical industry.
The work-sharing initiative coordinates the assessment of a NAS application that has been filed in at least two jurisdictions.

2.2 Indication and Dosage

2.2.1 Requested Indication

Vabysmo is a bispecific inhibitor of angiopoietin-2 (Ang-2) und VEGF (vascular endothelial growth factor) for the treatment of:

- neovascular (wet) age-related macular degeneration (nAMD)
- diabetic macular oedema (DME)

2.2.2 Approved Indication

Treatment of neovascular (wet) age-related macular degeneration (nAMD).
Treatment of diabetic macular oedema (DME).

2.2.3 Requested Dosage

Summary of the applied standard dosage:

nAMD

The recommended dose of Vabysmo is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days or monthly) for the first 4 doses, followed by 6 mg (0.05 mL solution) administered by intravitreal injection at up to 16 weeks (every 4 months). Some patients will require dosing every 4 weeks (approximately every 28 ± 7 days or monthly). Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion.

DME

The recommended dose of Vabysmo is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days or monthly) for the first 4 doses, followed by 6 mg (0.05 mL solution) administered by intravitreal injection at up to 16 weeks (every 4 months). Some patients will require dosing every 4 weeks (approximately every 28 ± 7 days or monthly). The dosing interval can be adjusted by 4 weeks at a time. Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion.

Duration of treatment

Vabysmo is intended for long-term treatment.

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2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	22 June 2021
Formal control completed	4 August 2021
List of Questions (LoQ)	2 December 2021
Answers to LoQ	31 January 2022
Predecision	15 March 2022
Answers to PreDecision	6 April 2022
Final Decision	25 May 2022
Decision	approval

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3 Quality Aspects

3.1 Drug Substance

Swissmedic has not assessed the primary data relating to the drug substance and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

Faricimab is a humanised bispecific antibody that selectively binds vascular endothelial growth factor (VEGF)-A and angiopoein-2 (Ang-2). It is composed of two different heavy chains and two different light chains. One arm of the antibody binds VEGF-A and the other arm binds Ang-2. The constant region is based on a human IgG1 framework. Modifications to faricimab prevent it binding to the neonatal Fc receptor, Fc gamma receptors and C1 q.

Faricimab is produced in a Chinese hamster ovary (CHO) cell line.

3.2 Drug Product

The faricimab drug product is provided as a sterile, colourless to brownish-yellow solution for injection. It contains no preservatives. Each single-use, 2 mL vial contains 6 mg (nominal) of faricimab at target pH 5.5 in 0.05 mL solution. A volume overfill ensures that the declared quantity can be delivered. The drug product is formulated as 120 mg/mL faricimab. The excipients – L-histidine, acetic acid 30%, L-methionine, sodium chloride, D-sucrose, polysorbate 20 and water for injection – are of compendial grade and commonly used for the formulation of biopharmaceuticals.

The container closure system consists of a type I glass vial with a fluororesin-laminated butyl rubber stopper and crimped with an aluminium seal fitted with a plastic flip-off cap.

The faricimab drug product is co-packaged with a transfer filter needle (18 G 1x1/2''stainless steel transfer filter needle with 5 µm filter). The medical device is CE marked.

Several changes were made to the formulation and manufacturing process of the drug product during clinical development. Comparability studies between the different processes were performed.

The type I glass vial and the butyl rubber stopper are commonly used, and the materials meet compendial requirements.

Compatibility studies using the transfer filter needle have been conducted.

The drug product manufacturing process consists of thawing and pooling of the drug substance, bioburden reduction filtration, sterile filtration, aseptic filling and stoppering, capping and crimping, and visual inspection.

Suitable process controls are proposed.

The validation for the drug manufacturing process was performed with three process performance qualification batches covering the proposed batch size range.

The specifications for release of the drug product include relevant tests and acceptance criteria, e.g. for appearance, pH, osmolality, identity, purity and impurities, quantity, potency (both targets), visible and subvisible particles, bacterial endotoxins and sterility. The drug product specifications comply with current compendial or regulatory guidelines.

Batch analysis data from development, clinical and process performance qualification batches were provided. All batch release data comply with the drug product specifications valid at the time of batch release.

The vials are stored at 2 – 8°C protected from light. The stability data support a shelf life of 30 months.

3.3 Quality Conclusions

Satisfactory and consistent quality of the drug substance and drug product have been demonstrated. Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

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4 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Vabysmo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

Vabysmo®

Composition

Active substances

Faricimabum (genetically produced in CHO [Chinese Hamster Ovary] cells).

Excipients

L-histidinum, acidum aceticum, L-methioninum, polysorbatum 20 (manufactured from genetically modified maize), natrii chloridum, saccharum (manufactured from genetically modified sugar beet), aqua ad iniectabile.

One single-dose (0.05 mL solution for injection) contains 0.028 mg sodium.

Pharmaceutical form and active substance quantity per unit

Solution for injection in a vial for intravitreal use.
One mL Vabysmo solution for injection contains 120 mg faricimabum (120 mg/mL).
Vabysmo solution for injection is a clear to opalescent, colorless to brownish-yellow solution in a single-dose glass vial, containing 28.8 mg faricimab in 0.24 mL solution. This provides a usable quantity for injection of 0.05 mL solution containing 6 mg of faricimab as a single dose.

Indications/Uses

Treatment of neovascular (wet) age-related macular degeneration (nAMD).

Treatment of diabetic macular edema (DME).

Dosage/Administration

General

For intravitreal injection only. Vabysmo must be administered by a qualified physician experienced in intravitreal injections. Each vial should only be used for the treatment of a single eye.

Neovascular (wet) age-related macular degeneration (nAMD)

The recommended dose for Vabysmo is 6 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days, monthly) for the first 4 doses, followed by 6 mg (0.05 mL) via intravitreal injection at a dosing interval of up to every 16 weeks (4 months). The dosing interval should be based on the physician's judgment of the individual patient's retinal thickness (*Central Subfield Thickness*, CST) and/or visual acuity. Some patients may be dosed as frequently as every 4 weeks (approximately every 28 ± 7 days, monthly).
Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion.

Diabetic macular edema (DME)

The recommended dose for Vabysmo is 6 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days ± 7 days, monthly) for the first 4 doses. Thereafter, treatment may be individualised using a treat-and-extend approach. Based on the physician's judgement of the individual patient's CST and/or visual acuity, the dosing interval may be extended up to a maximum of every 16 weeks (4 months), in increments of up to 4 weeks. The treatment interval is to be shortened accordingly in the event of deterioration in the CST and/or visual acuity (see section «Properties/Effects, Pharmacodynamics»).
Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion, but there is no requirement for monthly monitoring between injections.
To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment.

Duration of treatment

Vabysmo is intended for long-term treatment.

Dose adjustment following undesirable effects/interactions

No dose modifications of Vabysmo are recommended.

Patients with hepatic disorders

No specific studies in patients with hepatic impairment have been conducted with Vabysmo (see «Pharmacokinetics, Kinetics in specific patient groups»).

However, no dose adjustment is required in patients with hepatic impairment.

Patients with renal disorders

No specific studies in patients with renal impairment have been conducted with Vabysmo (see «Pharmacokinetics, Kinetics in specific patient groups»).

However, no dose adjustment is required in patients with renal disorders.

Elderly patients

In the four Phase III clinical studies, approximately 60% (1,149/1,929) of patients randomized to treatment with Vabysmo were ≥ 65 years of age. Population pharmacokinetic analysis has shown an effect of age on ocular pharmacokinetics of faricimab. But the effect was considered not clinically meaningful. No significant differences in efficacy or safety of faricimab were determined with increasing age in these studies. No dose adjustment is required in patients ≥ 65 years of age (see «Pharmacokinetics, Kinetics in specific patient groups»).

Children and adolescents

The safety and efficacy of Vabysmo in pediatric patients have not been established.

Special patient groups

No special dosage modification is required for any of the populations that have been studied (e.g., elderly, gender, race).

Delayed administration

If an injection is delayed or missed, the patient should return to be assessed by physician at the next available visit and continue dosing depending on physician’s discretion.

If visual and/or anatomic outcomes indicate that the patient is not benefitting from continued treatment, Vabysmo should be discontinued.

Mode of administration

Vabysmo should be inspected visually for particulate matter and discoloration prior to administration.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. Sterile equipment for paracentesis should be available in the event it is required.

Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. vision loss, eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Comprehensive instructions for the administration of Vabysmo are given in the Instructions for Use (see «Instructions for Use»).

Contraindications

Vabysmo is contraindicated in patients with ocular or periocular infections.

Vabysmo is contraindicated in patients with active intraocular inflammation.

Vabysmo is contraindicated in patients with known hypersensitivity to faricimab or any of the excipients. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

Warnings and precautions

Intravitreal injection-related reactions

Intravitreal injections, including those with Vabysmo have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment and retinal tear. Proper aseptic injection techniques must always be used when administering Vabysmo. Patients should be instructed to report any symptoms, such as pain, loss of vision, photophobia, blurred vision, floaters, or redness, suggestive of endophthalmitis or any of the above-mentioned events without delay, to permit prompt and appropriate management.

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including those with Vabysmo. Special precaution is needed in patients with poorly controlled glaucoma (do not inject Vabysmo while the IOP is ≥ 30 mmHg). In all cases, both the IOP and perfusion of the optic nerve head and/or vision must be monitored and managed appropriately.

Systemic effects

Systemic adverse events including arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may be related to VEGF inhibition.

Immunogenicity

The active substance in Vabysmo is a therapeutic protein. An immunological reaction to Vabysmo is therefore possible. Patients should be instructed to report any signs or symptoms of intraocular inflammation such as vision loss, eye pain, increased sensitivity to light, floaters or worsening eye redness, which might be a clinical sign attributable to hypersensitivity.

Bilateral Treatment

The safety and efficacy of Vabysmo administered in both eyes have not been studied.

Concomitant use of other anti-VEGF medicinal products

There are no data available on the concomitant use of Vabysmo with anti-VEGF medicinal products in the same eye.

Withholding treatment

Treatment should be withheld in patients with:

- Rhegmatogenous retinal detachment, stage 3 or 4 macular holes, retinal tear; treatment should not be resumed until an adequate repair has been performed.
- Treatment related decrease in Best Corrected Visual Acuity (BCVA) of ≥ 30 letters compared with the last assessment of visual acuity; treatment should not be resumed earlier than the next scheduled treatment.
- Performed or planned intraocular surgery within the previous or next 28 days; treatment should not be resumed earlier than the next scheduled treatment.

Retinal pigment epithelial tear

Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for nAMD include a large and/or high pigment epithelial detachment. When initiating Vabysmo therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

Populations with limited data

There is only limited experience in the treatment of DME patients with HbA1c over 10%, patients with high-risk proliferative diabetic retinopathy (DR), or nAMD and DME patients with active systemic infections. There is also no experience with the treatment with Vabysmo of diabetic patients with uncontrolled hypertension with Vabysmo. This lack of information should be considered by the physician when treating such patients.

Drug Abuse and Dependence

There is no evidence that Vabysmo has the potential for drug abuse and dependence.

Other information

Vabysmo solution for injection for intravitreal use contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially «sodium-free».

Interactions

No drug-drug interaction studies have been performed with Vabysmo.

Pregnancy, lactation

Women of childbearing age

Women of childbearing potential should use effective contraception during treatment with Vabysmo and for at least 3 months following the last dose of Vabysmo.

Pregnancy

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

No adverse effects were observed in a study in pregnant cynomolgus monkeys (see «Preclinical data, Reproductive toxicity»).

VEGF inhibition has been shown to cause malformations, embryo-fetal resorption, and decreased fetal weight. VEGF inhibition has also been shown to affect follicular development, corpus luteum function, and fertility. No dedicated studies addressing the effects of Ang-2 inhibition on pregnancy are available. Based on non-clinical data, Ang-2 inhibition may lead to effects comparable to VEGF inhibition. Systemic exposure after ocular administration of Vabysmo is very low.

It is not known whether faricimab can cross the placenta or cause harm to the fetus when administered to pregnant women. Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. Although the systemic exposure after ocular administration is very low, faricimab should not be used during pregnancy unless that treatment is required due to the clinical condition of the woman.

Birth process

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

Lactation

It is not known whether Vabysmo is excreted in human breast milk. No studies have been conducted to assess the impact of Vabysmo on milk production or its presence in breast milk. Because many drugs are excreted in human milk with the potential for absorption and harm to infant growth and development exists, caution should be exercised when Vabysmo is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Vabysmo and any potential adverse effects on the breastfed child from Vabysmo.

Fertility

No reproductive or fertility studies have been conducted. No effects on reproductive organs were observed in a 6-month cynomolgus monkey study at faricimab doses up to 3 mg/eye (8-10x clinical exposures based on AUC). VEGF inhibition has been shown to affect follicular development, corpus luteum function and fertility. Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is

a potential risk to female reproductive capacity, and to embryo-fetal development, however the risk is considered low due to the low systemic exposure after ocular administration.

Effects on ability to drive and use machines

Vabysmo may have a minor influence on the ability to drive and use machines due to possible temporary visual disturbances following the intravitreal injection and the associated eye examination. Patients should not drive or use machines until visual function has recovered sufficiently.

Undesirable effects

Summary of the safety profile

All safety data were derived from actively controlled (aflibercept) phase III studies.

A total of 3,213 patients constituted the safety population in the four Phase III clinical studies (1,926 Vabysmo treated patients; 664 in nAMD and 1,262 in DME). The most serious adverse reactions were cataract (0.9%), uveitis (0.5%), endophthalmitis (0.3%), vitritis (0.3%), retinal tear (0.2%) and rhegmatogenous retinal detachment (< 0.1%).

The most frequently reported adverse reactions in patients treated with Vabysmo were cataract (11%), conjunctival hemorrhage (7%), IOP increased (4%), vitreous floaters (4%), eye pain (3%) and retinal pigment epithelial tear (nAMD only) (3%).

List of adverse reactions

The safety data described below include all adverse reactions from the pooled data across four Phase III clinical studies in the indications nAMD and DME, with a reasonable possibility of causality attribution to the injection procedure or medicinal product. The adverse reactions are listed according to the MedDRA system organ class and ranked by frequency using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000).

Table 1: Summary of adverse reactions occurring in patients treated with Vabysmo in phase III clinical trials

Adverse reactions	Vabysmo N = 1,926	Frequency category
Eye Disorders		
Cataract	10.7%	Very common
Conjunctival hemorrhage	7.3%	Common
Intraocular pressure increased	3.6%	Common

Vitreous floaters	3. 6%	Common
RPE tear (nAMD only)	2.9%	Common
Eye pain	2.5%	Common
Lacrimation increased	1.1%	Common
Ocular discomfort	0.9%	Uncommon
Eye irritation	0.8%	Uncommon
Eye pruritus	0.8%	Uncommon
Corneal abrasion	0.7%	Uncommon
Ocular hyperemia	0.6%	Uncommon
Vision blurred	0.6%	Uncommon
Visual acuity reduced	0.5%	Uncommon
Uveitis	0.5%	Uncommon
Iridocyclitis	0.4%	Uncommon
Iritis	0.4%	Uncommon
Sensation of foreign body	0.4%	Uncommon
Vitreous haemorrhage	0.4%	Uncommon
Endophthalmitis	0.3%	Uncommon
Vitritis	0.3%	Uncommon
Conjunctival hyperaemia	0.2%	Uncommon
Retinal tear	0.2%	Uncommon
Rhegmatogenous retinal detachment	< 0.1%	Rare

Visual acuity reduced transiently	< 0.1%	Rare

Description of specific adverse reactions and other information

There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. A low incidence rate of arterial thromboembolic events was observed in the Vabysmo clinical trials in patients with nAMD and DME. Across indications no notable difference between the groups treated with Vabysmo and the comparator were observed.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Doses higher than the recommended dosing regimen have not been studied. Overdosing with greater than recommended injection volume may increase intraocular pressure.

In the event of an overdose, IOP should be monitored and, if deemed necessary by the treating physician, appropriate treatment should be initiated.

Properties/Effects

ATC code

S01LA09

Mechanism of action

Faricimab is a humanized bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct pathways by neutralization of both Ang-2 and vascular endothelial growth factor A (VEGF-A). Ang-2 causes vascular instability by promoting endothelial destabilization, pericyte loss, and pathological angiogenesis, thus potentiating vascular leakage and inflammation. It also sensitizes blood vessels to the activity of VEGF-A resulting in further vascular destabilization. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularization. By dual inhibition of

Ang-2 and VEGF-A, faricimab reduces vascular permeability and inflammation, inhibits pathological angiogenesis and restores vascular stability.

Pharmacodynamics

In the four phase III studies described in the following, a decrease in the median ocular concentrations of free ANG-2 and free VEGF-A was detected from Day 7 compared to baseline.

nAMD
Similar reductions in the mean thickness of the central region of the fovea (central subfield thickness, CST) were observed from baseline through week 48 with Vabysmo, and were comparable to those observed with aflibercept. The mean CST reduction from baseline to the primary endpoint visits (averaged at weeks 40, 44 and 48) was -137 µm and -137 µm for Vabysmo dosed at intervals of 8 weeks (q8w), 12 weeks (q12w) or 16 weeks (q16w) versus -129 µm and -131 µm with the use of aflibercept in the TENAYA and LUCERNE studies, respectively. There was a comparable effect of Vabysmo and aflibercept on the reduction of intraretinal fluid (IRF), subretinal fluid (SRF), and pigment epithelial detachment (PED). At the primary endpoint visits, the proportion of patients in the TENAYA and LUCERNE studies, respectively, with absence of IRF was 76%-82% and 78%-85 % under treatment with Vabysmo vs. 74%-85% and 78%-84% under treatment with aflibercept. The percentage of patients with absence of SRF in both studies was 70%-79% and 66%-78% under treatment with Vabysmo vs. 66%-78% and 62%-76% under treatment with aflibercept. The percentage of patients with absence of PED in both studies was 3%-8% and 3%-6% under treatment with Vabysmo vs. 8%-10% and 7%-9% under treatment with aflibercept.

At week 48, comparable changes from baseline in total area of lesions due to choroidal neovascularisation (CNV) and comparable reductions in CNV leakage area with excretion of blood and fluid were observed in both studies for patients under treatment with Vabysmo and aflibercept.

DME
Reductions in mean CST from baseline observed in both the YOSEMITE study and the RHINE study were numerically greater in patients treated with Vabysmo every 8 weeks (q8w) and Vabysmo up to q16w adjustable dosing as compared to aflibercept q8w from week 4 to week 100. Greater proportions of patients in both Vabysmo arms achieved absence of IRF and absence of DME (defined as reaching CST below 325 µm on OCT) over time in both studies, compared to the aflibercept arm. Comparable reductions in SRF were observed across the respective Vabysmo and aflibercept treatment arms over time in both studies. The mean reduction of CST from baseline to the primary endpoint visits (averaged at weeks 48, 52 and 56) in the YOSEMITE study was 207 µm and 197 µm in patients treated with Vabysmo q8w and Vabysmo up to q16w adjustable dosing compared to 170 µm in patients treated with aflibercept q8w; results were 196 µm, 188 µm and 170 µm, respectively in

the RHINE study. These mean CST reductions were maintained through year 2. The proportions of patients with absence of DME at primary endpoint visits (min-max) in the YOSEMITE study were 77%-87% and 80%-82% in patients treated with Vabysmo q8w and Vabysmo up to q16w adjustable dosing, respectively, as compared to 64%-71% in patients treated with aflibercept q8w; results were 85%-90%, 83%-87%, and 71%-77%, respectively in the RHINE study. These results were maintained through year 2.
In the YOSEMITE study, the proportions of patients with absence of IRF at primary endpoint visits (averaged at weeks 48, 52 and 56) were 42%-48% and 34%-43% in patients treated with Vabysmo q8w and Vabysmo up to q16w adjustable dosing, respectively, as compared to 22%-25% in patients treated with aflibercept q8w; results were 39%-43 %, 33%-41%, and 23%-29%, respectively in the RHINE study. These results were maintained through year 2.

Clinical efficacy

Treatment of neovascular (wet) age-related macular degeneration (nAMD)

The safety and efficacy of faricimab were evaluated in two 2-arm, randomised (1:1), multicentre, double-masked studies (TENAYA and LUCERNE) in patients with nAMD compared to anti-VEGF treatment. Treatment (faricimab 6 mg or aflibercept 2 mg) was administered by intravitreal injection, initially at 4-week intervals. In the aflibercept arm, the dosing interval after 3 initial aflibercept injections was 8 weeks for the remainder of the study (q8w). In the faricimab arm, the dosing interval was individually adjusted after 4 initial doses. The final (fixed) dosing interval was 8 weeks (q8w), 12 weeks (q12w) or a maximum of 16 weeks (q16w) depending on protocol defined CST change as measured on SD-OCT and/or BCVA change as measured by ETDRS letter scores, as well as treating physician clinical assessment of the presence/absence of macular haemorrhage at weeks 20 and 24.

The trials included a total of 1,329 treatment-naïve patients, of whom 1,326 received at least one dose (including 664 patients in the faricimab arm). The average age [age range] of the population studied was 75.9 years [50 to 99 years]. The primary efficacy endpoint was the mean change from the baseline in BCVA within the first year (based on the mean over weeks 40, 44 and 48) determined using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart at a distance of 4 metres. In both studies, the primary hypothesis (non-inferiority) was confirmed: Patients treated with Vabysmo at an interval up to q16w and patients treated with aflibercept q8w exhibited a comparable mean change from their respective baseline in BCVA.

The proportion of patients on each of the different treatment intervals at week 48 in the TENAYA and LUCERNE studies, respectively was:

- q16w: 46 %, 45 %

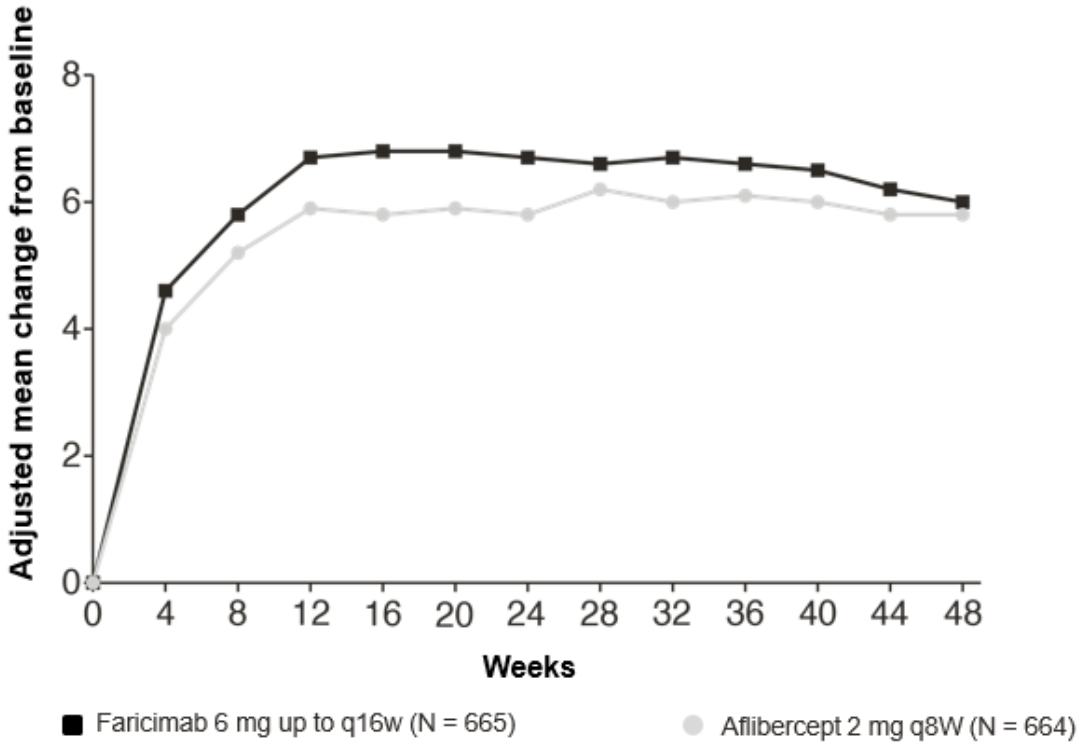
- q12w: 34 %, 33 %
- q8w: 20 %, 22 %

Table 2: Efficacy outcomes at the primary endpoint visits[a] in TENAYA and LUCERNE

Efficacy Outcomes	TENAYA		LUCERNE	
	Vabysmo up to q16w N = 334	Aflibercept q8w N = 337	Vabysmo up to q16w N = 331	Aflibercept q8w N = 327
Mean change in BCVA as measured by ETDRS letter score from baseline (95% CI)	5.8 (4.6, 7.1)	5.1 (3.9, 6.4)	6.6 (5.3, 7.8)	6.6 (5.3, 7.8)
Proportion of patients with ≥ 15 letter gain from baseline (CMH weighted proportion, 95% CI)	20.0% (15.6%, 24.4%)	15.7% (11.9%, 19.6%)	20.2% (15.9%, 24.6%)	22.2% (17.7%, 26.8%)
Proportion of patients avoiding ≥ 15 letter loss from baseline (CMH weighted proportion,95% CI)	95.4% (93.0%, 97.7%)	94.1% (91.5%, 96.7%)	95.8% (93.6%, 98.0%)	97.3% (95.5%, 99.1%)

[a] Average of weeks 40, 44 and 48.
BVCA: Best Corrected Visual Acuity.
ETDRS: Early Treatment Diabetic Retinopathy Study.
CI: Confidence Interval.
CMH: Cochran–Mantel–Haenszel method; a statistical test that generates an estimate of an association with a binary outcome and is used for assessment of categorical variables.

Figure 1: Pooled Phase III nAMD Studies (TENAYA and LUCERNE): Plot of Change from Baseline in BCVA in the Study Eye through Week 48: MMRM Method (Primary Estimand) (ITT Population)



In both the TENAYA and LUCERNE studies, improvements from baseline in BCVA and CST at week 60 were comparable across the two treatment arms and consistent with those seen at week 48.

Efficacy results in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, lesion type, lesion size) in each study, and in the pooled analysis, were consistent with the results in the overall populations.

In both studies, Vabysmo administered at intervals of up to q16w demonstrated clinically meaningful improvements from baseline to week 48 in the National Eye Institute Visual Function Questionnaire (NEI VFQ -25) composite score that were comparable to aflibercept q8w. Patients in Vabysmo arms in the TENAYA and LUCERNE studies achieved a ≥ 4-point improvement from baseline in the NEI VFQ -25 composite score at week 48.

Treatment of diabetic macular oedema (*DME)*

The safety and efficacy of faricimab were evaluated in two 3-arm, randomised (1:1:1), multicentre, double-masked studies (YOSEMITE and RHINE) conducted over a period of 2 years in patients with DME comparative to anti-VEGF treatment. Patients in the three study arms received intravitreal injections of faricimab 6 mg q8w (after 6 monthly injections at the start of the treatment), faricimab 6 mg with personalised injection interval up to a maximum of q16w (after 4 monthly injections at the start of the treatment or aflibercept 2 mg q8w (after 5 monthly injections at the start of the treatment).

In the faricimab arm with extended dosing up to every 16 weeks, the dosing followed a standardized treat-and-extend approach. Based on CST change as measured on OCT and/or BCVA change as measured by ETDRS letter score, the personalised injection interval in the faricimab group could be extended by 4 weeks or shortened by 4 or 8 weeks at each of the study drug dosing visits (see «Dosage/Administration»).

The trials included a total of 1,891 patients (of whom approximately 94% had type 2 diabetes mellitus), with 1,622 (85.8%) patients completing the studies through week 100. A total of 1,887 were treated with at least one dose through week 56 (1,262 with Vabysmo). The mean age [age range] of the patients studied was 62.2 years [24 to 91 years]. The study population included both anti-VEGF naïve patients (78%) and patients with previous anti-VEGF therapy (22%).
The primary efficacy endpoint was the mean change in BCVA from baseline to the end of the first year (mean of at weeks 48, 52 and 56) determined using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart at a distance of 4 metres. In both studies, the primary hypothesis (non-inferiority) was confirmed for both treatment arms: patients treated with Vabysmo q8w or patients treated with Vabysmo on extended dosing up to q16w had a comparable mean change from baseline in BCVA, as patients treated with aflibercept q8w at year 1, and these vision gains were maintained through year 2.

After 4 initial monthly doses, the patients in the Vabysmo arm with up to q16w adjustable dosing interval could have received a total of at least 6 and a maximum of 21 injections through week 96. At week 52, 74% and 71%, respectively of patients in the respective Vabysmo arms with up to q16w adjustable dosing in the YOSEMITE and RHINE studies achieved a dosing interval of q16w or q12w (53% and 51% on q16w, 21% and 20% on q12w). Of these patients in the YOSEMITE and RHINE studies, respectively, 75% and 84% maintained ≥ q12w dosing without an interval reduction below q12w through week 96; of the patients on q16w at week 52, 70% and 82% of patients maintained q16w dosing without an interval reduction through week 96. At week 96, 78% of patients in the respective Vabysmo arm with up to q16w adjustable dosing achieved a q16w or q12w dosing interval in both studies (60% and 65% on q16w, 18% and 14% on q12w). In 4% and 6% of patients in the YOSEMITE and RHINE studies, respectively, the interval was extended to q8w and the patients maintained a ≤ q8w dosing interval through week 96; 3% and 5% received only a q4w interval.

Detailed results from the analyses of the YOSEMITE and RHINE studies are listed in Table 3 and Figure 2 below.

Table 3: Efficacy outcomes at the year 1[a] and year 2[b] primary endpoint visits in the YOSEMITE and RHINE studies

Efficacy Outcomes	YOSEMITE					
	Year 1			Year 2		
	Vabysmo q8w N = 315	Vabysmo up to q16w adjustable dosing N = 313	Aflibercept q8w N = 312	Vabysmo q8w N = 262	Vabysmo up to q16w adjustable dosing N = 270	Aflibercept q8w N = 259
Mean change in BCVA as measured by ETDRS letter score from baseline (97.5 % CI year 1 and 95 % year 2)	10.7 (9.4, 12.0)	11.6 (10.3, 12.9)	10.9 (9.6, 12.2)	10.7 (9.4, 12.1)	10.7 (9.4, 12.1)	11.4 (10.0, 12.7)
Proportion of patients who gained at least 15 letters in BCVA from baseline (CMH weighted proportion, 95 % CI year 1 and year 2)	29.2% (23.9%, 34.5%)	35.5% (30.1%, 40.9%)	31.8% (26.6%, 37.0%)	37.2% (31.4%, 42.9%)	38.2% (32.8%, 43.7%)	37.4% (31.7%, 43.0%)
Proportion of patients who avoided loss of at least 15 letters in BCVA from baseline (CMH weighted proportion, 95 % CI year 1 and year 2)	98.1% (96.5%, 99.7%)	98.6% (97.2%, 100.0%)	98.9% (97.6%, 100.0%)	97.6% (95.7%, 99.5%)	97.8% (96.1%, 99.5%)	98.0% (96.2%, 99.7%)

Efficacy Outcomes	RHINE					
	Year 1			Year 2		
	Vabysmo q8w N = 317	Vabysmo up to q16w adjustable dosing N = 319	Aflibercept q8w N = 315	Vabysmo q8w N = 259	Vabysmo up to q16w adjustable dosing N = 282	Aflibercept q8w N = 254
Mean change in BCVA as measured by ETDRS letter score from baseline (97.5 % CI year 1 and 95 % year 2)	11.8 (10.6, 13.0)	10.8 (9.6, 11.9)	10.3 (9.1, 11.4)	10.9 (9.5, 12.3)	10.1 (8.7, 11.5)	9.4 (7.9, 10.8)

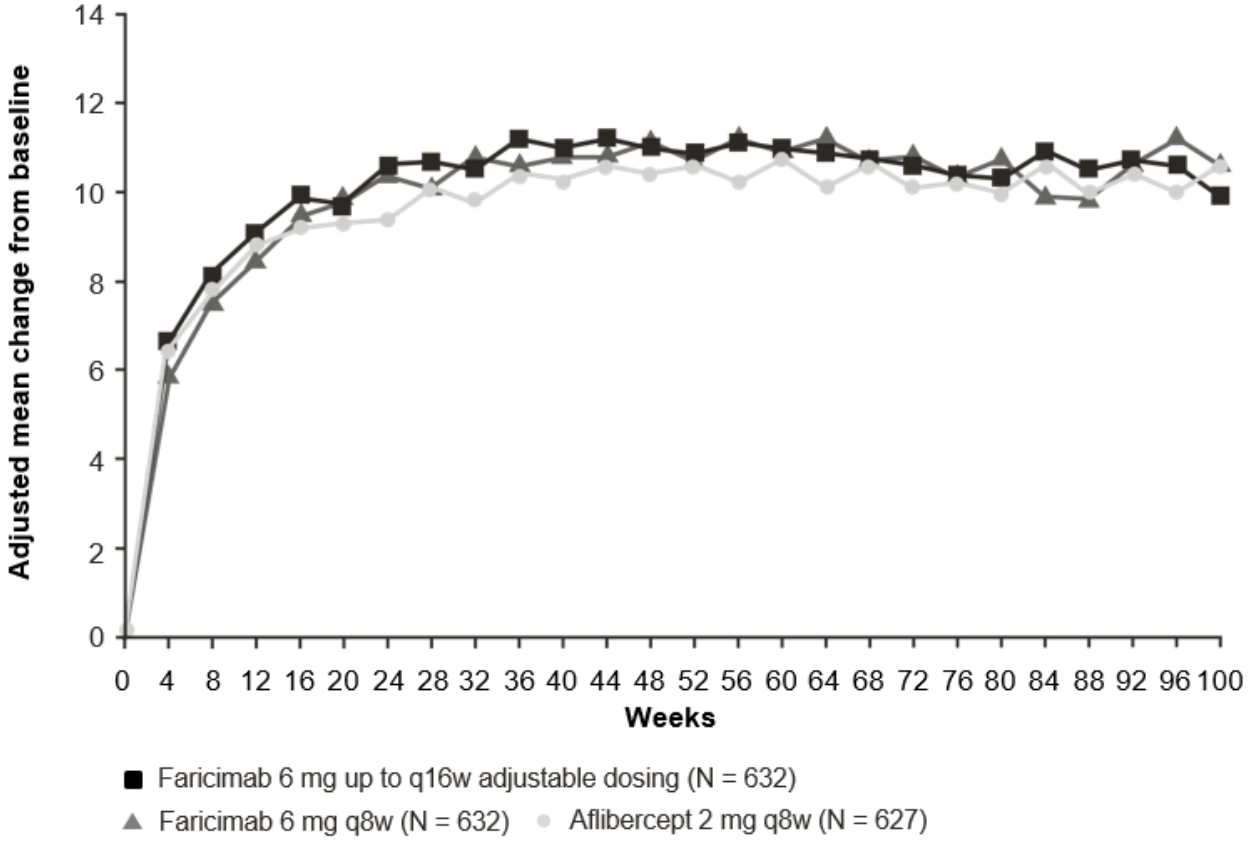
Efficacy Outcomes	RHINE					
	Year 1			Year 2		
	Vabysmo q8w N = 317	Vabysmo up to q16w adjustable dosing N = 319	Aflibercept q8w N = 315	Vabysmo q8w N = 259	Vabysmo up to q16w adjustable dosing N = 282	Aflibercept q8w N = 254
Proportion of patients who gained at least 15 letters in BCVA from baseline (CMH weighted proportion, 95 % CI year 1 and year 2)	33.8% (28.4%, 39.2%)	28.5% (23.6%, 33.3%)	30.3% (25.0%, 35.5%)	39.8% (34.0%, 45.6%)	31.1% (26.1%, 36.1%)	39.0% (33.2%, 44.8%)
Proportion of patients who avoided loss of at least 15 letters in BCVA from baseline (CMH weighted proportion, 95 % CI year 1 and year 2)	98.9% (97.6%, 100.0%)	98.7% (97.4%, 100.0%)	98.6% (97.2%, 99.9%)	96.6% (94.4%, 98.8%)	96.8% (94.8%, 98.9%)	97.6% (95.7%, 99.5%)

Efficacy Outcomes	YOSEMITE					
	52 weeks			96 weeks		
	Vabysmo q8w n = 237	Vabysmo up to q16w adjustable dosing n = 242	Aflibercept q8w n = 229	Vabysmo q8w n = 220	Vabysmo up to q16w adjustable dosing n = 234	Aflibercept q8w n = 221
Proportion of patients with ≥2-step ETDRS-DRSS improvement from baseline (CMH weighted proportion)	46.0%	42.5%	35.8%	51.4%	42.8%	42.2%

Efficacy Outcomes	RHINE					
	52 weeks			96 weeks		
	Vabysmo q8w n = 237	Vabysmo up to q16w adjustable dosing n = 242	Aflibercept q8w n = 229	Vabysmo q8w n = 220	Vabysmo up to q16w adjustable dosing n = 234	Aflibercept q8w n = 221
Proportion of patients with ≥2-step ETDRS-DRSS improvement from baseline (CMH weighted proportion)	44.2%	43.7%	46.8%	53.5%	44.3%	43.8%

[a] Average of weeks 48, 52, 56; [b]Average of weeks 92, 96, 100.
BVCA: Best Corrected Visual Acuity.
ETDRS: Early Treatment Diabetic Retinopathy Study.
CI: Confidence Interval.
CMH: Cochran–Mantel–Haenszel method; a statistical test that generates an estimate of an association with a binary outcome and is used for assessment of categorical variables.
Note: The CMH-weighted % data shown for the aflibercept arm are for the comparison between Vabysmo q8w and aflibercept, however the corresponding CMH-weighted % for Vabysmo adjustable vs. aflibercept comparison is similar to the one shown above.
ETDRS-DRSS: Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale (Scale for evaluation of diabetic retinopathy from the Early Treatment Diabetic Retinopathy Study).

Figure 2: Pooled Phase III DME Studies (YOSEMITE and RHINE): Plot of Change from Baseline in BCVA in the Study Eye through Week 100: MMRM Method (Primary Estimand) (ITT Population)



Efficacy results in patients who were anti-VEGF treatment naive prior to study participation and in all the other evaluable subgroups (e.g. by age, gender, race, baseline HbA1c, baseline visual acuity) in each study were consistent with the results in the overall populations.

The treatment effect was independent of glycaemic management, and comparable outcomes were achieved with faricimab treatment in patients whose HbA1c improved or worsened by > 0.5 % over time, or stayed within 0.5 % of baseline.

Elderly patients

In the four Phase III clinical studies, approximately 60% (1,149/1,929) of patients randomized to treatment with Vabysmo were ≥ 65 years of age. Population pharmacokinetic analysis has shown an effect of age on ocular pharmacokinetics of faricimab, which was not considered clinically meaningful (see «Dosage/Administration, Elderly patients» and «Pharmacokinetics, Elderly patients»).

Paediatrics

The safety and efficacy of Vabysmo in pediatric patients have not been established.

Further information

Immunogenicity

There is a potential for an immune response in patients treated with Vabysmo (see «Warnings and precautions»).

After dosing with Vabysmo for up to 48 (nAMD) and 100 (DME) weeks, treatment-emergent anti-faricimab antibodies were detected in approximately 10% of patients. The clinical significance of anti-faricimab antibodies regarding safety is unclear at this time. Among the patients with anti-faricimab antibodies, a higher incidence of intraocular inflammation adverse reactions were observed. However, the overall incidence of anti-faricimab antibody positivity and intraocular inflammation in the entire trial population is approximately 1%. Anti-faricimab antibodies were not associated with an impact on clinical efficacy or systemic pharmacokinetics.

Pharmacokinetics

Absorption

Vabysmo is administered intravitreally (IVT) to exert local effects in the eye. There have been no clinical studies performed with other routes of administration.

Based on a population pharmacokinetic analysis (including nAMD and DME N = 2,246), maximum free (unbound to VEGF-A and Ang-2) faricimab plasma concentrations (C_{max}) are estimated to occur

approximately 2 days post-dose. Mean (± SD) free plasma C_{max} are estimated 0.23 (0.07) µg/mL and 0.22 (0.07) µg/mL respectively in nAMD and in DME/DR patients. After repeated administrations, mean plasma free faricimab trough concentrations are predicted to be 0.002-0.003 µg/mL for q8w dosing.

Faricimab exhibited dose-proportional pharmacokinetics (based on C_{max} and AUC) over the dose range 0.5 mg-6 mg. There was no accumulation of faricimab in the vitreous or in plasma following monthly dosing based on exposure estimates from the population pharmacokinetic model.

Distribution

No information.

Metabolism

The metabolism of faricimab has not been directly studied. Faricimab is assumed to be catabolised into small peptides and amino acids in lysosymes, similar to endogenous IgG molecules.

Elimination

The faricimab plasma concentration-time profile declined in parallel with the vitreous and aqueous concentration-time profiles. The estimated mean ocular half-life and apparent systemic half-life of faricimab are each 7.5 days.

Kinetics in specific patient groups

Hepatic impairment

No formal pharmacokinetic study has been conducted in patients with hepatic impairment.

Renal impairment

No formal pharmacokinetic study has been conducted in patients with renal impairment. Pharmacokinetic analysis of patients in all clinical studies including 857 patients with mild, 532 with moderate and 37 with severe renal function disorder revealed no differences with respect to systemic pharmacokinetics of faricimab after intravitreal administration of Vabysmo.

Elderly patients

In the four Phase III clinical studies, approximately 60 % (1,149/1,929) of patients randomized to treatment with Vabysmo were ≥ 65 years of age. Population pharmacokinetic analysis has shown an effect of age on ocular pharmacokinetics of faricimab, which was however not considered clinically meaningful.

Children and adolescents

The safety and efficacy of Vabysmo in pediatric patients have not been established.

Other demographic factors

Population pharmacokinetic analysis has shown an effect of body weight on systemic pharmacokinetics of faricimab. This effect was considered not clinically meaningful; no dose adjustment is needed.

A population-kinetic analysis provides no indication for any influences based on race or gender on the systemic pharmacokinetics of Vabysmo.

Preclinical data

Genotoxicity

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

Carcinogenicity

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

Fertility

No effects on reproductive organs were observed in a 6-month cynomolgus monkey study at faricimab doses up to 3 mg/eye (8-10x clinical exposures based on AUC).

Reproductive toxicity

No effects on pregnancy or fetuses were observed in an embryo-fetal development study in pregnant cynomolgus monkeys given 5 weekly intravenous injections of Vabysmo starting on day 20 of gestation at 1 mg/kg or 3 mg/kg. Serum exposure (C_{max}) in monkeys at the no observed adverse effect level (NOAEL) dose of 3 mg/kg was more than 500 times that in humans at a dose of 6 mg given by intravitreal injection once every 4 weeks.

Other information

Preparation for Administration

Vabysmo is a sterile, preservative-free, clear to opalescent, colorless to brownish-yellow solution.

Vabysmo should be inspected visually upon removal from the refrigerator and prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

The contents of the vial and transfer filter needle are sterile and for single use only. Do not use if the packaging, vial and/or transfer filter needle are damaged or expired.

Use aseptic technique for preparation of the intravitreal injection.

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the pack.

Special precautions for storage

Store in a refrigerator at 2-8 °C. Do not shake. Do not freeze.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Prior to use, the unopened vial of Vabysmo may be kept at room temperature, 20 °C to 25 °C, for up to 24 hours.

Ensure that the injection is given immediately after preparation of the dose.

Instructions for handling

See «Dosage/Administration» for dosing instructions.

For detailed instructions on administration, see «Instructions for Use».

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

- Needles and syringes should never be reused.

- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

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

Authorisation number

68395 (Swissmedic).

Packs

Vabysmo 28.8 mg/0.24 mL, solution for injection in a vial incl. 1 filter needle: 1 [B]

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd, Basel.

Date of revision of the text

May 2022.

Instructions for Use

The following information is intended for healthcare professionals only:

Before you start:

- Read all the instructions carefully before using Vabysmo.
- The Vabysmo kit includes a glass vial and transfer filter needle. The glass vial contains a single dose only. The filter needle is for single use only.
- Vabysmo should be stored refrigerated at temperatures between 2 °C to 8 °C.

  Do not freeze.

  Do not shake.
- Allow Vabysmo to reach room temperature, 20 °C to 25 °C before proceeding with the administration. Keep the vial in the original carton to protect from light.
- The Vabysmo vial may be kept at room temperature for up to 24 hours.
- The Vabysmo vial should be inspected visually prior to administration. Vabysmo is a clear to opalescent and colorless to brownish-yellow liquid solution.

  Do not use if particulates, cloudiness, or discoloration are visible.

  Do not use if the packaging, vial and/or transfer filter needle are expired, opened, or have been tampered with (see **Figure A**).
- Use aseptic technique to carry out the preparation of the intravitreal injection.

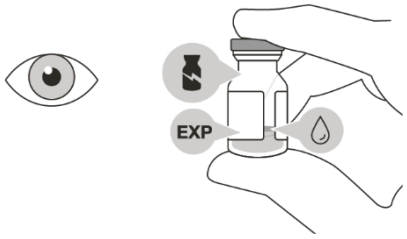


Figure A

Instructions for use of vial:

1. Gather the following supplies:

- One Vabysmo vial (included)
- One sterile 5-micron blunt transfer filter needle 18-gauge x 1½ inch, 1.2 mm x 40 mm (included)
- One sterile 1 mL Luer lock syringe with a 0.05 mL dose mark (**not included**)
- One sterile injection needle 30-gauge x ½ inch (**not included**)

  Note that a 30-gauge injection needle is recommended to avoid increased injection forces that could be experienced with smaller diameter needles.
- Alcohol swab (**not included**).

2. To ensure all liquid settles at the bottom of the vial, place the vial upright on a flat surface (for about 1 minute) after removal from packaging, to ensure all liquid settles at the bottom of the vial (see **Figure B**). Gently tap the vial with your finger (see **Figure C**), as liquid may stick to the top of the vial.

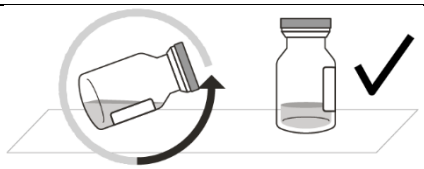


Figure B

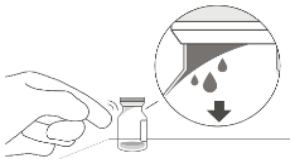


Figure C

3. Remove the flip-off cap from the vial (see **Figure D**) and wipe the vial septum with an alcohol swab (see **Figure E**).

Figure D

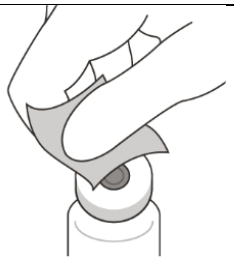


Figure E

4. Aseptically and firmly attach the included 18-gauge x 1½ inch transfer filter needle onto a 1 mL Luer lock syringe (see **Figure F**).

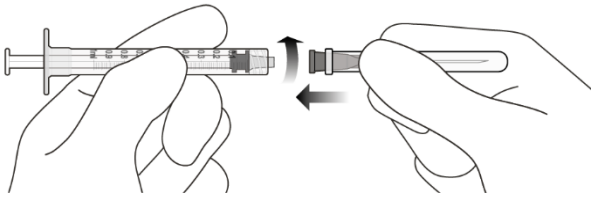


Figure F

5. Using aseptic technique, push the transfer filter needle into the centre of the vial septum (see **Figure G**), push it all the way in, then tilt the vial slightly so that the needle touches the bottom edge of the vial (see **Figure H**).

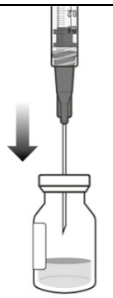


Figure G

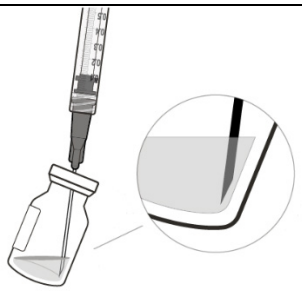


Figure H

6. Hold the vial slightly inclined and **slowly** withdraw all the liquid from the vial (see **Figure I**). Keep the bevel of the transfer filter needle submerged in the liquid, to avoid introduction of air.

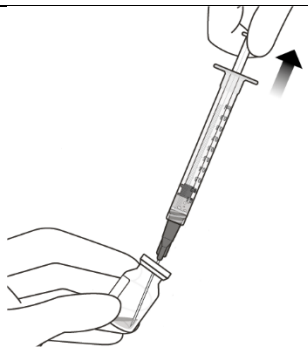


Figure I

7. Ensure that the plunger rod is drawn sufficiently back when emptying the vial, in order to completely empty the transfer filter needle (see **Figure I**).

8. Disconnect the transfer filter needle from the syringe and dispose of it in accordance with local regulations.

Do not use the transfer filter needle for the intravitreal injection.

9. Aseptically and firmly attach a 30-gauge x ½ inch injection needle onto the Luer lock syringe (see **Figure J**).

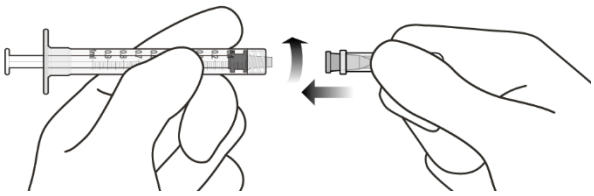


Figure J

10. Carefully remove the plastic needle shield from the needle by pulling it straight off.

11. To check for air bubbles, hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see **Figure K**).

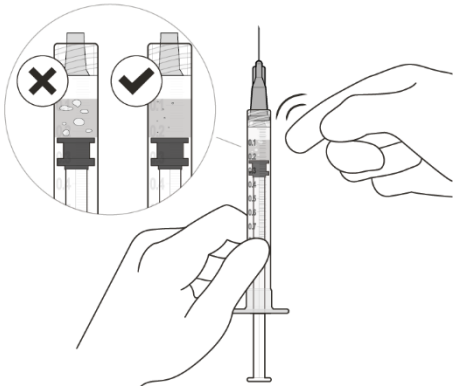


Figure K

12. Carefully expel the air from the syringe and needle, and **slowly** depress the plunger to align the rubber stopper tip to the 0.05 mL dose mark. The syringe is ready for the injection (see **Figure L**). Ensure that the injection is given **immediately** after preparation of the dose.

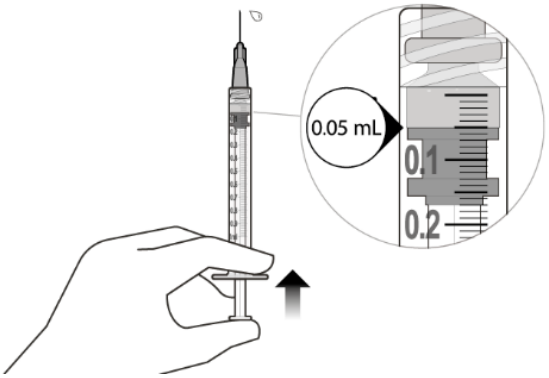


Figure L

13. Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.05 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel.

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