▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION - SYFOVRE® (PEGCETACOPLAN), SOLUTION FOR INJECTION

WARNING

Intravitreal pegcetacoplan is associated with the development of neovascular (wet) AMD which is a vision-threatening condition. Use of this medicine requires close monitoring by both ophthalmologist and patient. Treatment with anti-VEGF should be given separately from SYFOVRE administration (see *section 4.4 Special Warnings and Precautions for Use*).

1 NAME OF THE MEDICINE

Pegcetacoplan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 150 mg/mL pegcetacoplan solution. .

Each vial allows for the delivery of a single dose of 0.1 mL solution containing 15 mg pegcetacoplan.

For the full list of excipients, see section 6.1. List of Excipients.

3 PHARMACEUTICAL FORM

Solution for injection for intravitreal use.

Clear, colourless to light yellow aqueous solution.

SYFOVRE solution for injection does not contain any antimicrobial preservatives. The vial is for single use in one eye for one patient on one occasion only. Discard any residue.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SYFOVRE is indicated for the treatment of adult patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) with an intact fovea and when central vision is threatened by GA lesion growth.

The benefits and risks of intravitreal pegcetacoplan should be discussed with the patient prior to commencing treatment. SYFOVRE should be administered by an eye specialist experienced in the management of geographic atrophy.

4.2 DOSE AND METHOD OF ADMINISTRATION

SYFOVRE is for intravitreal injection only.

SYFOVRE must only be administered by a qualified health care provider (HCP) experienced in administering intravitreal injections.

Dosage

The dose for SYFOVRE is 15 mg (0.1 mL of 150 mg/mL solution) administered as a single intravitreal injection to each affected eye once every other month (approximately 60 days).

Special Populations

Elderly

The elderly population has been studied in clinical studies. No dose adjustment is required.

Renal impairment

No formal studies have been conducted with SYFOVRE in patients with renal impairment. No dose adjustment or special considerations are anticipated for patients with renal impairment (see *section 5.2 Pharmacokinetic Properties*).

Hepatic impairment

No formal studies have been conducted with SYFOVRE in patients with hepatic impairment. No dose adjustment or special considerations are anticipated for patients with hepatic impairment (see *section 5.2 Pharmacokinetic Properties*).

Paediatric Population

The safety and effectiveness of SYFOVRE in paediatric patients have not been established.

Method of Administration

Single use vial for intravitreal injection in one eye only.

Only 0.1 mL (15 mg SYFOVRE) should be administered to deliver a single dose. Any excess volume must be disposed.

Prior to the intravitreal injection, patients should be monitored for elevated intraocular pressure (IOP) using tonometry (see *section 4.4 Special Warnings and Precautions for Use*). If necessary, ocular hypotensive medication can be given to lower the IOP.

The intravitreal injection procedure must be carried out under aseptic conditions, which may include the use of surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anaesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid, and ocular surface should be administered prior to the injection, in accordance with standard medical practice. Prior to intravitreal injection procedure, the eye should be softened with a cotton-tipped applicator saturated with sterile topical anaesthetic drops by pushing against the globe with the swab at the planned injection site for 30-60 seconds to prevent potential increase in IOP.

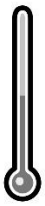
The injection needle should be inserted into the vitreous cavity, avoiding the horizontal meridian, and aiming towards the centre of the globe. Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.1 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel.

Immediately following the intravitreal injection, patients should be monitored for gross visual assessment. Additional evaluation may include checking for perfusion of the optic nerve head and tonometry.

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

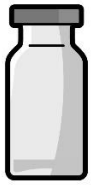
Each vial must be used only for the treatment of a single eye, as the extraction of multiple doses from a single vial may increase the risk of particulate or microbial contamination and subsequent infection. If the fellow eye requires treatment, a new sterile vial must be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles must be changed before SYFOVRE administration, to avoid contamination and infection risks. Repeat the same procedure steps as above.

Instructions for use and handling



Store SYFOVRE in the refrigerator between 2°C to 8°C; Keep the vial in the original carton to protect from light.

Remove the carton from the refrigerator. Keep the vial in the original carton at room temperature for at least 15 minutes prior to injection, but no longer than 8 hours. Fill the syringe immediately prior to the injection.



Do not shake the vial.

The vial is for single use in one eye only.

Inspect the solution. It is a clear, colorless to light yellow aqueous solution.

Do not use if:

- particulates, cloudiness, or discoloration are visible,
- the vial shows signs of damage or tampering,
- or if the expiration date has passed.

Use aseptic technique to carry out the following preparation steps:

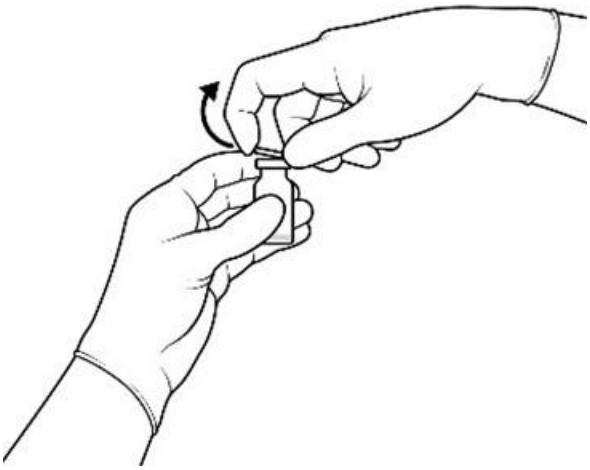
STEP 1:
Gather the supplies needed:

- One SYFOVRE vial (included)
- One sterile 5-micron filter needle (**not included**)
- One sterile 1 mL Luer-lock syringe with a 0.1 mL dose mark (**not included**)

- One sterile ½ inch: 29-gauge thin-wall injection needle with Luer-lock hub or a 27-gauge needle with Luer-lock hub (**not included**)
  Note: Increased injection forces and/or increased injection time could be experienced if a smaller diameter injection needle is used (e.g., 30-gauge)
- Alcohol swab (**not included**)

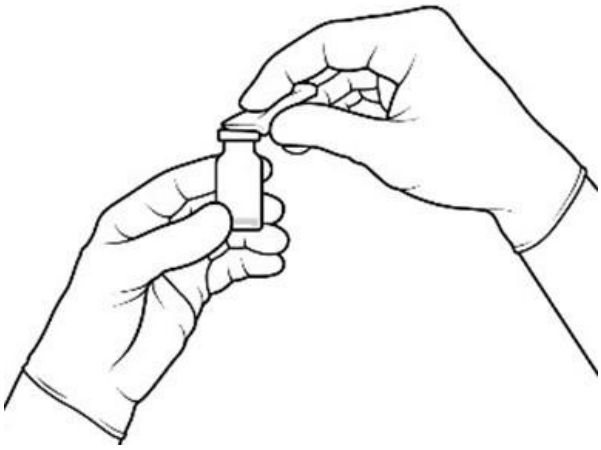
STEP 2:
Prepare the vial:
Remove the flip-off cap from the vial (see Figure 1).

Figure 1:



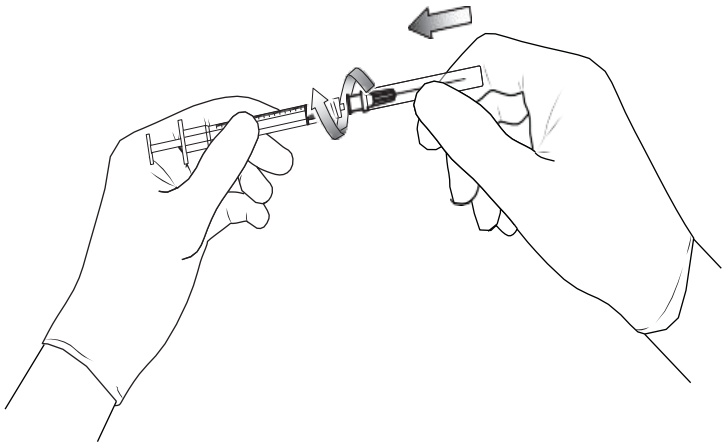
Clean the vial septum with an alcohol swab and wait for the alcohol to dry out (see Figure 2).

Figure 2:



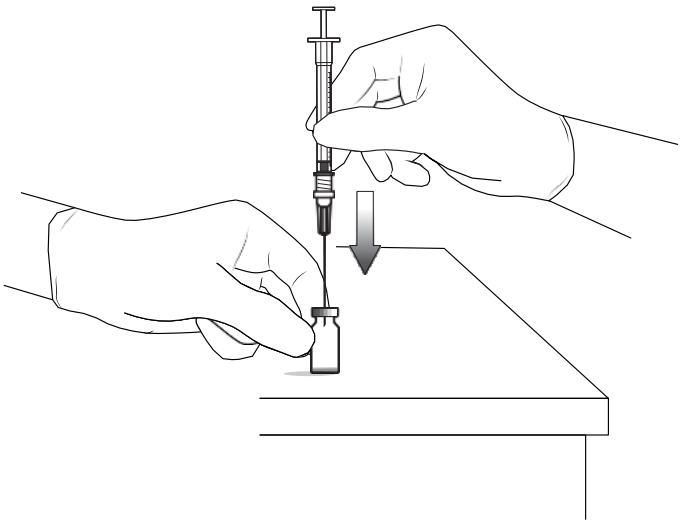
STEP 3
Attach the filter needle:
Attach the 5-micron filter needle to a 1 mL Luer-lock syringe by twisting it onto the Luer-lock syringe tip using aseptic technique. (see Figure 3).

Figure 3:



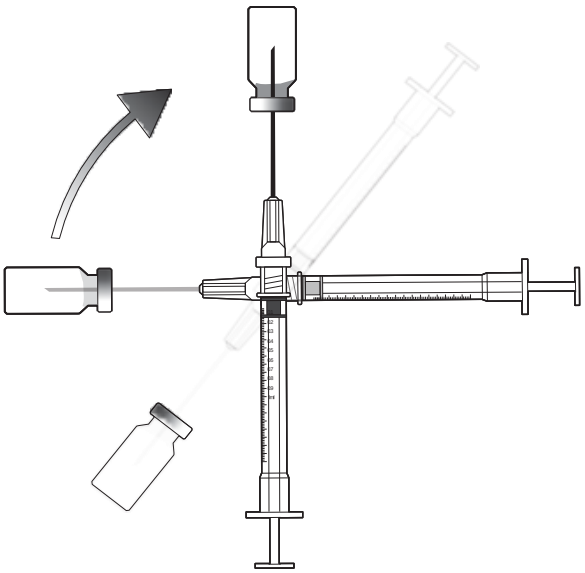
STEP 4
Withdraw the drug product:
Keep the vial on a flat working surface and insert the filter needle into the centre of the vial septum (see Figure 4).

Figure 4:



Keep the filter needle in the vial and turn the vial upside down (see Figure 5).

Figure 5:

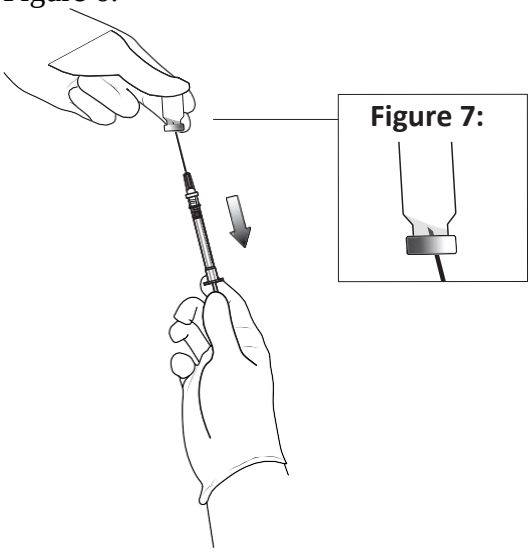


Slide the tip of the needle down so that it is submerged in the drug product.

Slightly tilt the vial and slowly pull back the plunger until the rubber stopper reaches the 0.3 mL mark on the syringe and allow the drug product to settle on top of the rubber stopper (see Figure 6).

Gradually retract the plunger to withdraw the remaining drug product. Ensure that the needle's tip remains constantly immersed in the drug product to avoid drawing excess air (see Figure 7).

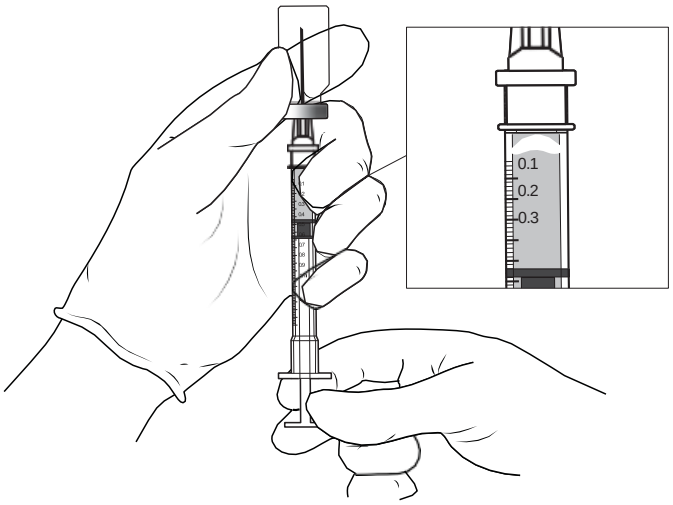
Figure 6:



*__Do not__ tap the syringe to remove air bubbles.

While maintaining the filter needle within the vial, move the plunger down and up until bubbles move to the top (see Figure 8).

Figure 8:



STEP 5
Remove the filter needle:
Using aseptic technique, disconnect the filter needle from the syringe.

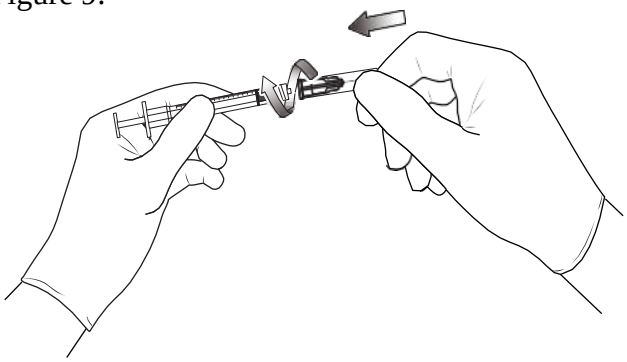
Discard the used filter needle into a sharps disposal container.

Do not use the filter needle for injection.

STEP 6
Attach the Injection Needle:

Aseptically and firmly assemble the injection needle onto the 1-mL Luer-lock syringe. (see Figure 9).

Figure 9:



STEP 7

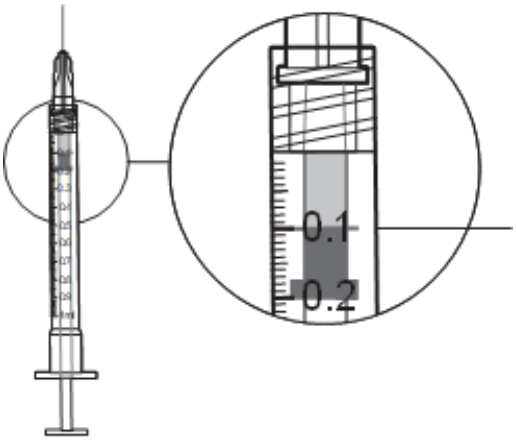
Set prescribed dose:

Check for air bubbles by holding the syringe with the needle pointing up.
*Do not tap the syringe to remove air bubbles.

If there are any air bubbles, remove the needle cap and with the needle end facing up gently advance the plunger to the 0.1 mL mark (See Figure 10). Only 0.1 mL (15 mg SYFOVRE) should be administered to deliver a single dose. Any excess volume must be disposed.

The syringe is ready for injection.

Figure 10:



Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.1 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel.

4.3 CONTRAINDICATIONS

SYFOVRE is contraindicated in patients with:

- Hypersensitivity to pegcetacoplan or to any of the excipients. Systemic hypersensitivity reactions (e.g., anaphylaxis, rash, urticaria) have occurred in patients treated with SYFOVRE.
- Ocular or periocular infections (see *section 4.4 Special Warnings and Precautions for Use*)
- Active intraocular inflammation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments (see *section 4.8 Adverse Effects*). Proper aseptic injection technique must always be used when administering SYFOVRE in order to minimise the risk of endophthalmitis

(*see Section 4.2 Dose and Method of Administration*). Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Once the event is considered clinically resolved, SYFOVRE treatment may be reinitiated.

Neovascular (wet) AMD

In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularisation (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24 (*see Section 4.8 Adverse Effects*). Patients with neovascular (wet) AMD in the fellow eye are at increased risk. Patients that are receiving SYFOVRE should be monitored with optical coherence tomography (OCT) and/or fluorescein angiography for signs of neovascular (wet) AMD and instructed to report any symptoms. In case anti-Vascular Endothelial Growth Factor (anti -VEGF) is required it should be given separately from SYFOVRE administration.

Increased Intraocular Pressure

Acute increase in intraocular pressure (IOP) may occur within minutes of any intravitreal injection, including with SYFOVRE (see *section 4.8 Adverse Effects*). Perfusion of the optic nerve head should be monitored and managed appropriately (see *section 4.2 Dose and Method of Administration*).

Intraocular Inflammation

In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare (see *section 4.8 Adverse Effects*). After inflammation resolves patients may resume treatment with SYFOVRE.

Retinal Vasculitis and/or Retinal Vascular Occlusion

In the post marketing setting, retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.

Use in the elderly

The elderly population has been studied in clinical studies. No dose adjustment is required.

Paediatric use

The safety and effectiveness of SYFOVRE in paediatric patients have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinical interaction studies have been performed. Nonclinical studies showed that pegcetacoplan has a low potential for pharmacokinetic drug interactions as it did not induce or inhibit cytochrome P450 isozyme activities or serve as a substrate and/or inhibitor for human drug transporters.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no fertility data in humans and no fertility studies have been performed with pegcetacoplan in animals. In general toxicity studies in rabbits and monkeys, doses of pegcetacoplan yielding systemic exposure orders of magnitude higher than in SYFOVRE patients produced no microscopic abnormalities in male and female reproductive organs to suggest potential impairment of fertility.

Women of childbearing potential

It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. For women planning to become pregnant, the use of SYFOVRE may be considered following an assessment of the risks and benefits.

Use in pregnancy – Category B3

There are no or limited amount of data on pegcetacoplan use in pregnant women. Studies in animals at high systemic exposures have shown harm to fetal development.

Animal Data

Pegcetacoplan treatment of pregnant monkeys at a subcutaneous dose of 28 mg/kg/day [yielding more than 500 times human exposure (AUC)] during organogenesis and through to parturition resulted in increased incidences of abortions and stillbirths. This increase in fetal loss occurred in the absence of maternotoxicity. No teratogenic effects were observed in offspring delivered at term and no developmental effects were observed in infants up to 6 months postpartum**.** Placental transfer of pegcetacoplan was shown to be minimal in monkeys (fetal serum concentration <1% of that in maternal serum; not pharmacologically significant).

Use in lactation

It is not known whether pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal intravitreal treatment is minimal, with excretion of pegcetacoplan in milk in monkeys demonstrated to be very limited (<1% of maternal serum concentration).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Injection with SYFOVRE has a minor influence on the ability to drive and use machines due to possible temporary visual disturbances associated either with the injection or the eye examination. Patients should not drive or use machines until their visual function has recovered sufficiently.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the Safety Profile from clinical trials
A total of 1258 patients constituted the safety population in the two Phase III studies (OAKS and DERBY). Among those, 839 patients were treated with the recommended dose of 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.

Most of the ocular adverse events were mild or moderate and 0.5% of patients experienced an ocular adverse event that led to study discontinuation. The most common adverse drug reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular (wet) AMD, vitreous floaters, vitreous detachment and conjunctival haemorrhage (see *section 4.4 Special Warnings and Precautions for Use*).

Serious adverse reactions in the study eye, reported in <1% of the patients treated with SYFOVRE, were endophthalmitis, uveitis, iridocyclitis, vitritis and retinal tear. Vitritis and retinal tear occurred only in the monthly dosing regimen.

Serious adverse reactions related to the injection procedure, which occurred in <0.1% of intravitreal injections with SYFOVRE, were endophthalmitis, retinal detachment, retinal tear, vitritis, and hyphaema. Retinal tear, vitritis and hyphaema occurred only in the monthly dosing regimen.

The safety profile seen in OAKS and DERBY at Month 12 was consistent with that seen at Month 24.

Tabulated summary of adverse reactions from clinical trials

The data described in Table 1 reflect exposure to SYFOVRE in a total of 839 patients with GA in two Phase III studies (OAKS and DERBY) through Month 24 (see *section 5.1 Clinical Trials*). The recommended dose of SYFOVRE is 15 mg every other month.

Table 1: Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with SYFOVRE Through Month 24 in Studies OAKS and DERBY

System organ class /Preferred term	PM	PEOM	Sham Pooled
	N = 419 n (%)	N = 420 n (%)	N = 417 n (%)
Eye Disorders			
Ocular discomfort*	56 (13)	42 (10)	45 (11)
Neovascular (wet) age-related macular degeneration*	51 (12)	28 (7)	13 (3)
Vitreous floaters	41 (10)	29 (7)	5 (1)
Conjunctival haemorrhage	34 (8)	34 (8)	15 (4)
Vitreous detachment	15 (4)	25 (6)	14 (3)
Retinal haemorrhage	18 (4)	21 (5)	12 (3)
Punctate keratitis*	23 (5)	11 (3)	3 (<1)
Posterior capsule opacification	15 (4)	15 (4)	11 (3)
Intraocular inflammation*	16 (4)	8 (2)	1 (<1)
Investigations			
Intraocular pressure increased	8 (2)	12 (3)	3 (<1)

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month
*The following reported terms were combined:
Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye
Neovascular (wet) age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularisation
Punctate keratitis included: punctate keratitis, keratitis
Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cell, iritis, anterior chamber flare

Neovascular (wet) AMD

Neovascular (wet) AMD was observed in 12% of patients treated with pegcetacoplan every month, 7% of patients treated with pegcetacoplan every other month and 3% in the control group by Month 24 in Phase III studies. Patients with presence of choroidal neovascularisation in the fellow eye had a higher incidence of neovascular (wet) AMD compared to patients with no choroidal neovascularisation in the fellow eye. The majority of the neovascular (wet) AMD events were mild to moderate in severity and all were non-serious. As part of clinical practice, active monitoring is suggested and treatment with anti-VEGF therapy may be recommended at the discretion of the physician (see *section 4.4 Special Warnings and Precautions for Use*).

Immunogenicity
As with all therapeutic peptides, there is a potential for immunogenicity. Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Anti-PEG and anti-pegcetacoplan peptide antibodies have been assessed for pegcetacoplan.

During the 24-month period in studies OAKS and DERBY, the incidence of anti-pegcetacoplan peptide antibodies in patients treated with pegcetacoplan was 4.3% (18/415 evaluable patients) and 2.5% (10/404 evaluable patients), respectively. Because of the low incidence of anti-pegcetacoplan peptide antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of pegcetacoplan is unknown.

During the 24-month treatment period in studies OAKS and DERBY, the incidence of anti-PEG antibodies in patients treated with pegcetacoplan was 10.2% /(42/412 evaluable patients) and 14.1% (57/404 evaluable patients)respectively. There was no identified clinically significant effect of anti-PEG antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of pegcetacoplan over the treatment duration of 24 months.

Postmarketing Experience

Eye disorders: Rare events of retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported spontaneously *(see section 4.4 Special Warnings and Precautions for Use).*

Systemic reactions: anaphylaxis, rash, and urticaria.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No case of overdose has been reported to date. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate treatment be instituted.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other ophthalmologicals, ATC code: S01XA31

Mechanism of action

Pegcetacoplan binds to complement protein C3 and its activation fragment C3b with high affinity thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation.

Overactivation of the complement system is strongly associated with the progression of GA. Increased levels of complement activity have been found in patients with GA, specifically in lesions and surrounding areas including photoreceptors. The complement C3 protein plays a role in driving the downstream damaging effects of complement overactivation in the progression of GA, which include uncontrolled inflammation, opsonisation, and retinal cell death. Pegcetacoplan acts centrally in the complement cascade by regulating C3, thereby exerting broad control of complement activation, and of the complement effectors that are involved in the pathogenesis of GA.

Pharmacodynamic effects

Cardiac Electrophysiology

Subcutaneous (SC) dosing of pegcetacoplan did not result in QT prolongation. Systemic exposures following IVT administration are much lower than with SC administration, therefore QT prolongation following IVT pegcetacoplan is not expected.

Postmarketing Experience

Not applicable

Clinical trials

The safety and efficacy of SYFOVRE were assessed in two multi-centre, randomised, sham-controlled Phase III studies in patients with GA secondary to AMD, with or without subfoveal involvement, with a total of 1258 randomised patients (SYFOVRE 839 patients, sham 419 patients). Studies OAKS (APL2-304) and DERBY (APL2-303) were 24 months in duration, in which patients received treatment for the entire length of the study.

Patient ages ranged from 60 to 100 years with a mean of 78.7 years. Mean (standard deviation) total area of GA lesion(s) at baseline in the study eye (in mm^2) were 8.23 (3.832), 8.29 (4.107), for OAKS, and DERBY, respectively.

In each study, patients were randomly assigned in a 2:2:1:1 ratio to 1 of 4 dosing regimens:

- 1) SYFOVRE administered at 15 mg/0.1 mL monthly;
- 2) SYFOVRE administered at 15 mg/0.1 mL every other month;
- 3) sham administered monthly;
- 4) sham administered every other month.

In the OAKS and DERBY studies, the primary efficacy endpoint was change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm^2) measured by fundus autofluorescence (FAF).

The recommended dose of SYFOVRE is every other month, however full trial results are presented.

At Month 12, there was a clinically meaningful reduction of GA lesion growth observed in both studies. The OAKS study met the primary endpoint and demonstrated a statistically significant difference in change from baseline through Month 12 in total area of GA lesions in the PM and PEOM groups compared to the sham pooled group. The DERBY study showed a numerically positive effect for PM and PEOM, compared to the sham pooled group, but missed statistical significance for the primary endpoint for both SYFOVRE treatment arms.

At Month 24, a sustained and persistent clinically meaningful effect was observed in reduction of GA lesion growth in OAKS and DERBY. The change from baseline through Month 24 in total area of GA lesions growth was reduced in the PM and PEOM groups compared to the sham pooled group in OAKS and DERBY.

Detailed results are shown in Table 2 and Figures 6 and 7.

Table 2: Analysis of Change from Baseline at Month 12 and Month 24 in Study Eye GA Lesion Area Measured by FAF in Studies OAKS, and DERBY

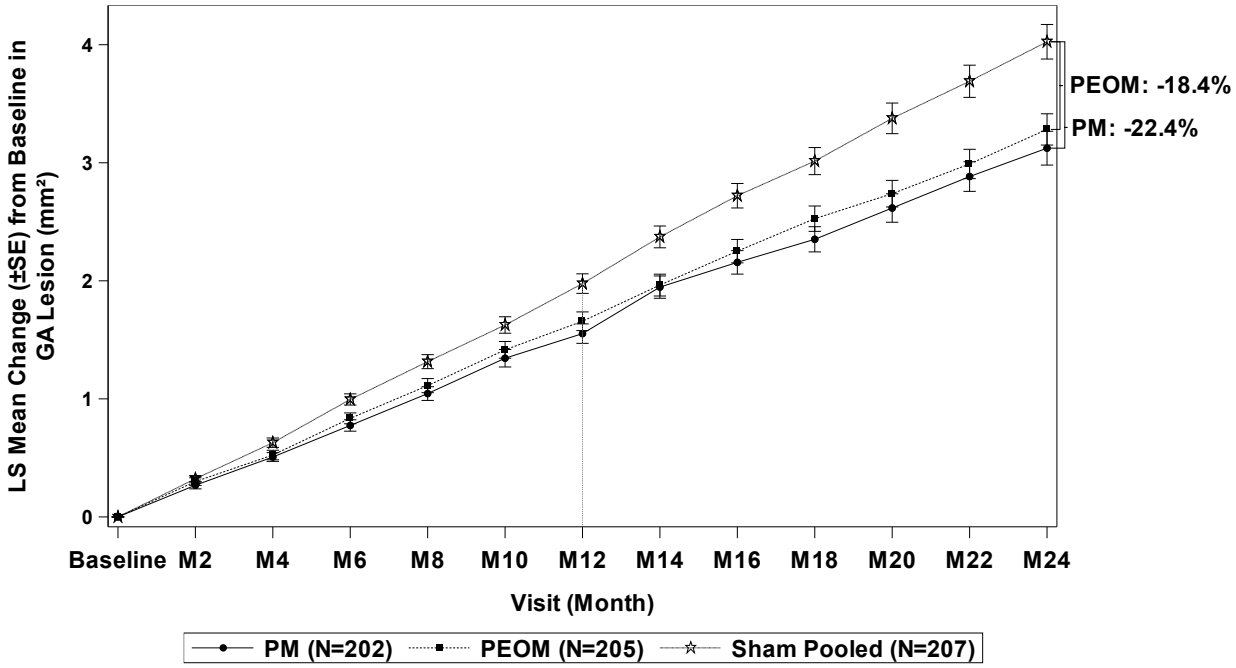
Study	Timepoint	Group	N	Change From Baseline in GA Lesion Area (mm^2)‡		
				LS Mean (SE)	LS Mean Difference (95% CI) Compared to Sham Pooled	Percent Difference Compared to Sham Pooled
OAKS	Month 12	PM	202	1.56 (0.084)	−0.41 (−0.64 to −0.18) p = 0.0004	−20.9%
		PEOM	205	1.65 (0.081)	−0.32 (−0.54 to −0.09) p = 0.0055	−16.1%
		Sham Pooled	207	1.97 (0.082)	NA	
	Month 24	PM	202	3.12 (0.143)	−0.90 (−1.30 to −0.50) p< 0.0001*	−22.4%
		PEOM	205	3.28 (0.132)	−0.74 (−1.13 to −0.36) p = 0.0002*	−18.4%
		Sham Pooled	207	4.03 (0.146)	NA	
DERBY	Month 12	PM	201	1.73 (0.079)	−0.23 (−0.47 to 0.01) p = 0.0615	−11.7%
		PEOM	201	1.76 (0.074)	−0.21 (−0.44 to 0.03) p = 0.0854	−10.6%
		Sham Pooled	195	1.96 (0.096)	NA	
	Month 24	PM	201	3.23 (0.125)	−0.75 (−1.15 to −0.34) p = 0.0004*	−18.8%
		PEOM	201	3.34 (0.130)	−0.63 (−1.05 to −0.22) p = 0.0030*	−15.9%
		Sham Pooled	195	3.97 (0.168)	NA	

GA: Geographic atrophy; FAF: fundus autofluorescence; PM: SYFOVRE monthly; PEOM: SYFOVRE every other month; SD: standard deviation; LS = least square; SE: standard error; CI: confidence interval

‡Based on a mixed effects model for repeated measures. For studies OAKS and DERBY, the model included effects for treatment, baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2), visit, presence of choroidal neovascularisation in the fellow eye (yes or no), visit by treatment interaction, and visit by baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) interaction.

*Month 24 p-values are not controlled for multiplicity.

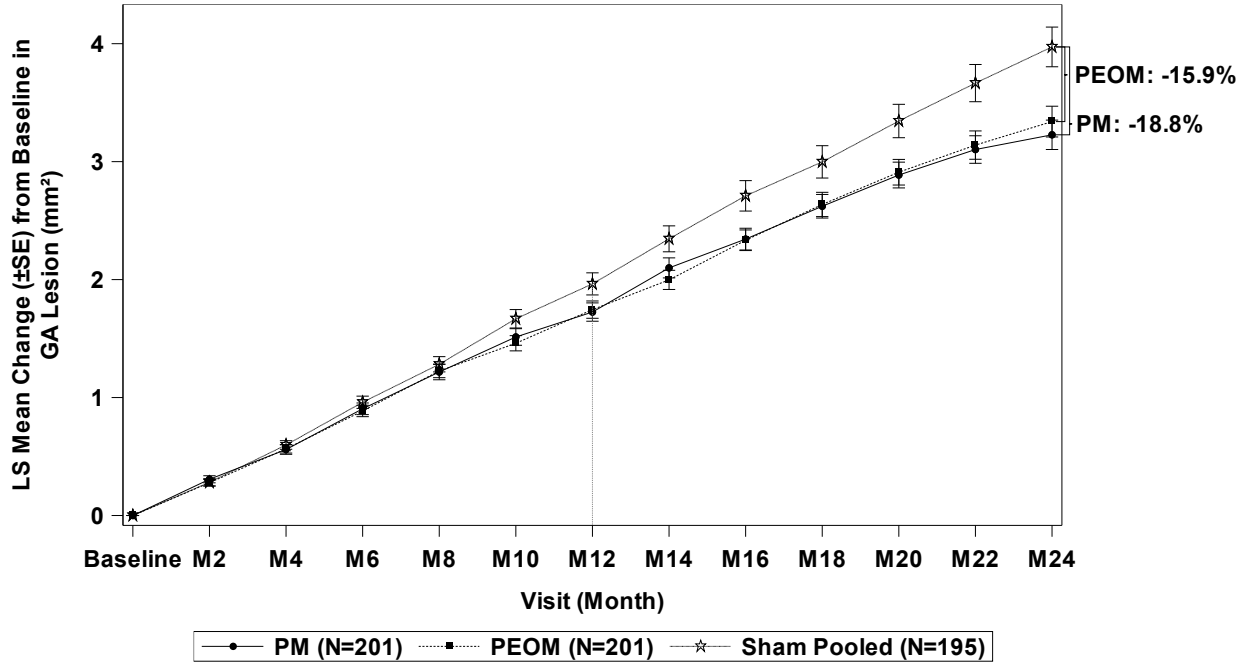
Figure 6: LS Mean Change from Baseline Through Month 24 in Study Eye GA Lesion Area Measured by FAF in OAKS



GA: Geographic atrophy; FAF: fundus autofluorescence; PM: SYFOVRE monthly; PEOM: SYFOVRE every other month; LS = least square; SE: standard error

Based on mixed effects model for repeated measures. The model included effects for treatment, baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2), visit, presence of choroidal neovascularisation in the fellow eye (yes or no), visit by treatment interaction, and visit by baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) interaction.

Figure 7: LS Mean Change from Baseline Through Month 24 in Study Eye GA Lesion Area Measured by FAF in DERBY



GA: Geographic atrophy; FAF: fundus autofluorescence; PM: SYFOVRE monthly; PEOM: SYFOVRE every other month; LS = least square; SE: standard error
Based on mixed effects model for repeated measures. The model included effects for treatment, baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2), visit, presence of choroidal neovascularisation in the fellow eye (yes or no), visit by treatment interaction, and visit by baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) interaction.

Treatment effects in evaluable subgroups (e.g., age, gender, GA lesion location, GA lesion focality) in each study were generally consistent with the results in the overall population.

Foveal involvement is a key predictor of GA lesion growth. The treatment effect at Month 24 in patients with GA without subfoveal involvement was -30.8% (OAKS), -22.0% (DERBY) in the PM group, and -17.3% (OAKS), -26.0% (DERBY) in the PEOM group compared to the sham pooled group. For patients with subfoveal involvement the treatment effect was -21.6% (OAKS), -15.5% (DERBY) in the PM group, and -22.2% (OAKS), -7.8% (DERBY) in the PEOM group compared to sham pooled group.

Consistent with the natural history of the disease, GA lesion enlargement was accompanied by a consistent decline in visual function over 24 months. In the prespecified analyses, no clinically meaningful differences were observed through Month 24 for the three groups in the key secondary functional endpoints (Best Corrected Visual Acuity, Reading speed, Functional Reading Independence Index, Microperimetry Mean Sensitivity) in both studies.

5.2 PHARMACOKINETIC PROPERTIES

SYFOVRE is administered directly into the vitreous to exert local effects in the eye.

Following repeat intravitreal administration of pegcetacoplan at a dose of 15 mg/0.1 mL, geometric mean (%CV) serum C_{max} value at steady state was 2.1 µg/mL (35.1%) and 1.6 µg/mL (34.0%) for GA patients dosed monthly and every other month, respectively. The steady state geometric mean (%CV) serum trough concentrations were 0.9 µg/mL (60.9%) and 0.2 µg/mL (101%) for patients treated monthly and every other month, respectively.

Absorption
Following intravitreal administration of pegcetacoplan, the systemic median T_{max} of pegcetacoplan is between 7 and 14 days.

Distribution
The estimated volume of distribution of pegcetacoplan is 1.83L in patients with GA following intravitreal administration.

Metabolism
Based on its PEGylated peptide structure, the metabolism of pegcetacoplan is expected to occur via catabolic pathways and be degraded into small peptides and amino acids.

Excretion
The estimated geometric mean (%CV) vitreous half-life is 13.2 days (35.9%). The estimated geometric mean (%CV) of clearance (CL) is 0.296 L/day (41.5%) and geometric mean systemic half-life of elimination ($t_{1/2}$) is 4.27 days (41.5%) in patients with GA.

Results of a radiolabeled study in monkeys suggest the primary route of elimination is via urinary excretion.

Linearity/Non-linearity
Following intravitreal treatment, systemic exposure of pegcetacoplan increases approximately proportionally over a dosage range from 4 to 20 mg.

Special Populations
There were no clinically significant differences on the pharmacokinetics of pegcetacoplan intravitreal administration based on age (60 to 97 years old), sex, renal impairment, and hepatic function as evaluated by total bilirubin (0.05-1.7 mg/dL), albumin (2.96-5.38 g/dL), aspartate aminotransferase (8.7-101 IU/L), or alanine aminotransferase (5.9-136 IU/L).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Pegcetacoplan was not mutagenic when tested in *in vitro* bacterial reverse mutation (Ames) assays and was not genotoxic in an *in vitro* assay in human TK6 cells or in an *in vivo* micronucleus assay in mice.

Carcinogenicity
Animal carcinogenicity studies with pegcetacoplan have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Trehalose dihydrate
Glacial acetic acid
Sodium acetate trihydrate
Sodium hydroxide (for pH adjustment)
Glacial acetic acid (for pH adjustment)
Water for injections

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C – 8°C in a refrigerator. Do not freeze.
Keep the vial in its original carton to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Sterile solution in a vial (Type I glass) with a stopper (cholorobutyl), and a seal (aluminium) with a flip-off cap (polypropylene).

Pack size of 1 vial.

6.6 SPECIAL PRECAUTIONS FOR USE, HANDLING AND DISPOSAL

The vial is for single use in one eye for one patient only.

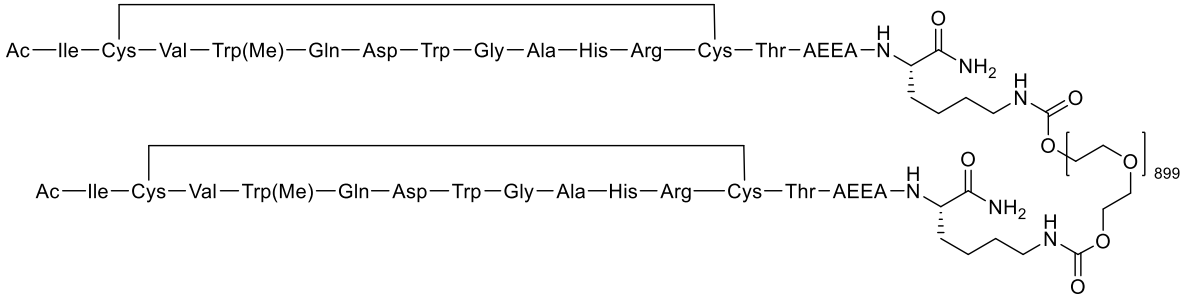
Since the vial contains more volume than the recommended dose (0.1 mL), a part of the volume contained in the vial has to be disposed after administration.

The solution should be inspected visually for any foreign particulate matter and/or discolouration or any variation in physical appearance prior to administration. In the event of either being observed, or if the vial shows signs of damage or tampering, dispose the medicinal product.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Pegcetacoplan, the active ingredient in SYFOVRE solution for intravitreal injection 150 mg/mL, is a symmetrical molecule composed of two identical pentadecapeptides covalently bound to both ends of a linear polyethylene glycol (PEG) molecule. The molecular weight of pegcetacoplan is approximately 43.5 kiloDaltons (kDa). The peptide moieties bind to complement C3 and exert a broad inhibition of the complement cascade. The 40-kDa PEG moiety imparts improved solubility and longer residence time in the body after administration of the drug product. The structure of pegcetacoplan is shown below.



The chemical name is poly(oxy-1,2-ethanediyl), α-hydro, ω-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-α-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-*N6*-carboxy-L-lysinamide cyclic (2→12)-(disulfide).

The chemical formula is $C_{170}H_{248}N_{50}O_{47}S_4 \cdot (C_2H_4O)_n$ n = 800-1100.

CAS registry number: 2019171-69-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Apellis Australia Pty Ltd
Level 3, 141 Camberwell Road
Hawthorn East VIC 3143
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Medical enquiries: 1800 879 456

9 DATE OF FIRST APPROVAL

29 January 2025

10 DATE OF REVISION

Not applicable.

Summary table of changes

Section changed	Summary of new information
1-10	New document