▼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 https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – IZERVAY™ (AVACINCAPTAD PEGOL) SOLUTION FOR INJECTION

WARNING: NEOVASCULAR (WET) AMD

Intravitreal Avacincaptad pegol may be associated with the development of neovascular (wet) AMD, which may be vision-threatening. Close monitoring is required. If neovascularisation develops, treatment with an anti-VEGF agent should be considered (see sections 4.4 and 4.8).

1 NAME OF THE MEDICINE

Avacincaptad pegol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL solution contains 20 mg of avacincaptad pegol (oligonucleotide basis) as avacincaptad pegol sodium.

Each vial contains 30.38 mg of avacincaptad pegol equivalent to 7.0 mg of oligonucleotide in 0.35 mL solution. This provides a usable amount to deliver a single dose of 0.1 mL solution containing 8.68 mg avacincaptad pegol equivalent to 2.0 mg of oligonucleotide. Each dose provides 2 mg avacincaptad pegol (oligonucleotide basis) in 0.1 mL solution.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection

Clear to slightly opalescent, colourless to slightly yellow solution with a target pH of 7.3.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

IZERVAY 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 (see Section 5.1 Pharmacodynamic properties – Clinical Trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection, once monthly for the first 12 months, followed by once monthly or every other month thereafter.

Clinical particulars

The benefits and risks of intravitreal IZERVAY should be discussed with the patient prior to commencing treatment. IZERVAY should be administered by an ophthalmologist experienced in the management of GA.

Special Populations

Paediatric population

The safety and efficacy of IZERVAY in paediatric patients have not been established.

Elderly

No dose adjustment is required in elderly patients.

Renal impairment

The safety and efficacy of avacincaptad pegol in patients with any degree of renal impairment have not been evaluated. No dose adjustment is recommended.

Hepatic impairment

The safety and efficacy of avacincaptad pegol in patients with any degree of hepatic impairment have not been evaluated. No dose adjustment is recommended.

Other Special Populations

The systemic pharmacokinetics of avacincaptad pegol are not influenced by race or sex. No dose adjustment is needed.

Delayed or Missed Dosing

If a dose is delayed or missed, the patient should return to their treating ophthalmologist at the next available visit to be assessed for continued treatment.

Method of Administration

IZERVAY is administered by intravitreal injection.

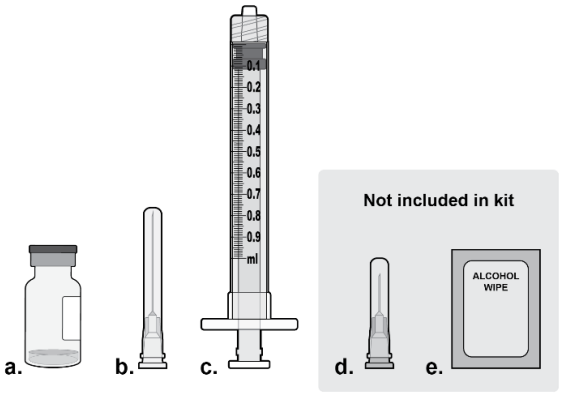
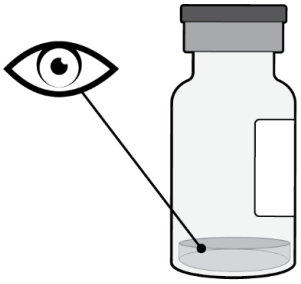
IZERVAY must be administered by an ophthalmologist experienced in administering intravitreal injections.

Prior to the intravitreal injection, patients should be assessed for elevated intraocular pressure (IOP), for example using tonometry (see section 4.4 Special warnings and precautions for use). If necessary, ocular hypotensive medication may be given to lower the IOP.

IZERVAY is for single use in one patient only. Discard any residue remaining in the vial.

Preparation for Administration

- Read all the instructions carefully before using IZERVAY.
- The IZERVAY kit includes a glass vial, filter needle, and an empty syringe. The glass vial, filter needle, and empty syringe are for single use only.
- Store IZERVAY in the refrigerator at temperatures between 2°C to 8°C. Do not freeze. Do not shake.
- Prior to use, allow IZERVAY to reach room temperature, 15°C to 25°C. The IZERVAY vial may be kept at room temperature for up to 24 hours. Keep the vial in the original carton to protect from light.
- Use aseptic technique to carry out the preparation of the intravitreal injection.
- Each vial should only be used for the treatment of a single eye.

Step 1: Gather Supplies Gather the following supplies (*see Figure A*): a. One IZERVAY vial (included) b. One sterile 5-micron filter needle 18-gauge x 1½ inch (included) c. One sterile 1 mL Luer lock syringe with a 0.1 mL dose mark (included) d. One sterile injection needle 30-gauge x ½ inch (not included) NOTE: a 30-gauge injection needle is recommended to avoid increased injection forces that could be experienced with smaller diameter needles. e. Alcohol swab (not included)	 **Figure A**
Step 2: Inspect Vial Inspect the liquid in the vial. It should be a clear to slightly opalescent, colourless to slightly yellow liquid solution (*see Figure B*). **Do not** use if particulates, cloudiness, or discoloration are visible. **Do not** use if the packaging, vial, filter needle, injection needle, and/or empty syringe are expired, damaged, or have been tampered with.	 **Figure B**

Step 3: Orient Vial

Place the vial upright on a flat surface for about 1 minute after removal from packaging to make sure all liquid settles at the bottom of the vial *(see Figure C).*

Gently tap the vial with your finger to remove any liquid that may stick to the top of the vial *(see Figure D).*

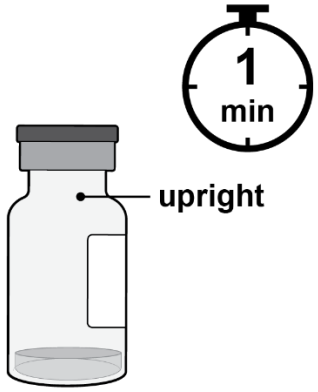


Figure C

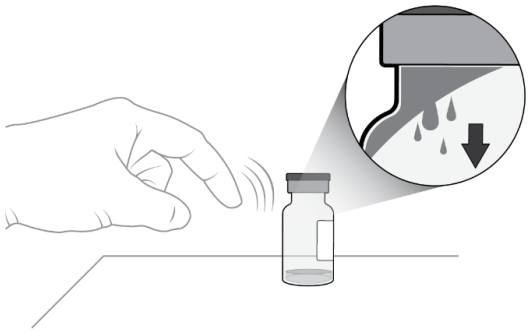


Figure D

Step 4: Clean Vial

Remove the flip-off cap from the vial (*see Figure E*).

Gently wipe the vial septum with an alcohol swab (*see Figure F*).

Figure E

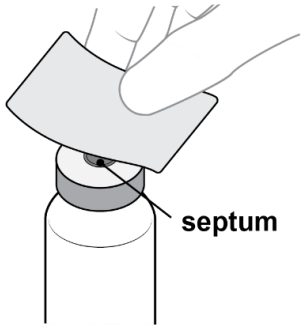


Figure F

Step 5: Attach Filter Needle

Using aseptic technique, firmly attach the included 18-gauge x 1½ inch filter needle onto the 1 mL Luer lock syringe and twist clockwise to secure *(see Figure G).*

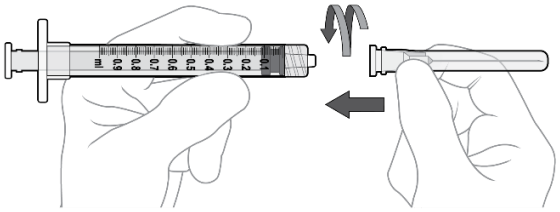


Figure G

Step 6: Insert Filter Needle into Vial

Using aseptic technique, push the filter needle all the way into the center of the vial septum *(see Figure H).*

Tilt the vial slightly so that the needle touches the bottom edge of the vial *(see Figure I).*
Rotate the filter needle so that the bevel is submerged into the liquid to avoid introduction of air.

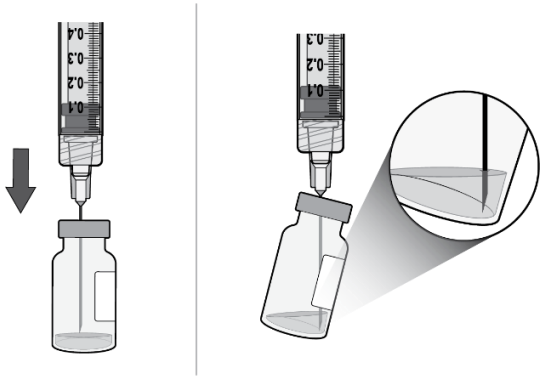


Figure H **Figure I**

Step 7: Withdraw Liquid

Slowly withdraw all the liquid from the vial (*see Figure J*).

Draw the plunger rod back far enough to completely empty the filter needle.

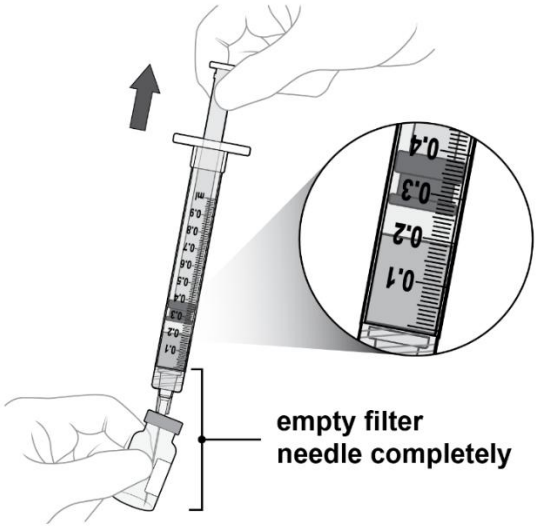
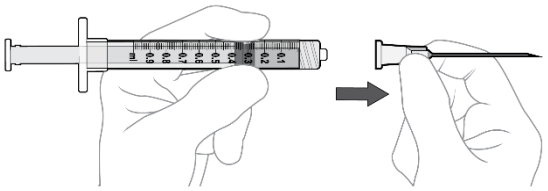
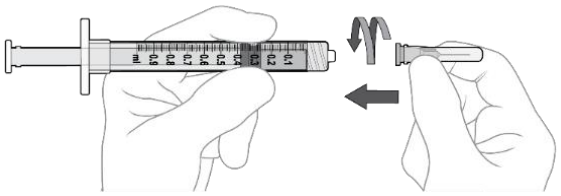
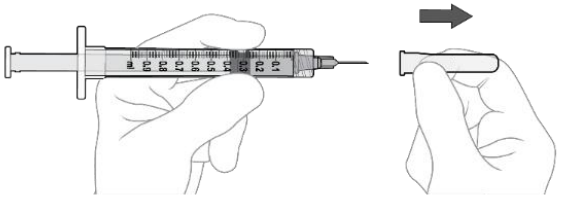
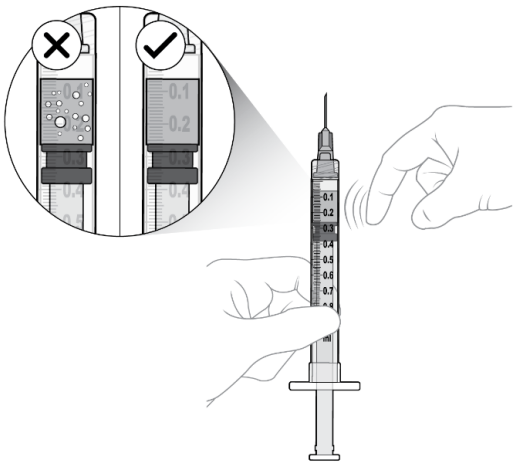
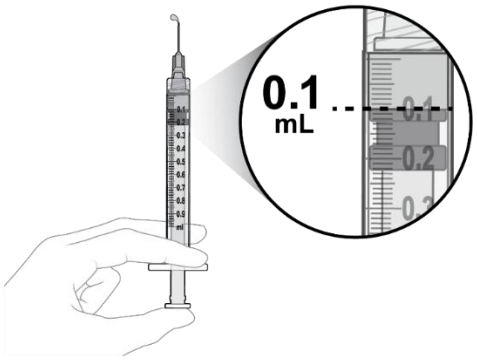


Figure J

Step 8: Disconnect Filter Needle Disconnect the filter needle from the syringe and dispose of it in accordance with local regulations (*see Figure K*). **Do not use the filter needle for the intravitreal injection.**	 **Figure K**
Step 9: Attach Injection Needle Using aseptic technique, firmly attach the 30-gauge x ½ inch injection needle onto the Luer lock syringe (*see Figure L*). Carefully remove the plastic needle shield from the needle by pulling it straight off (*see Figure M*).	 **Figure L**  **Figure M**
Step 10: Check Syringe Check for air bubbles by holding 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 N).*	 **Figure N**

Step 11: Prepare Appropriate Dose **Slowly** depress the plunger to: • Expel the air from the syringe. • Align the rubber stopper tip to the **0.1 mL** dose mark. The syringe is now ready for the injection *(see Figure O).* Make sure to give the injection immediately after preparing the dose.	 **Figure O**

Injection Procedure

The intravitreal injection procedure must be carried out under controlled aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis equipment (if required). Adequate anaesthesia and an appropriate topical antiseptic should be given prior to the injection. 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.

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

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure (IOP). Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available. Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., vision loss, eye pain, redness of the eye, photophobia, blurring of vision, flashes of light, an increased number of small particles or cobwebs in the vision, worsening of side vision, curtainlike shadow over the field of vision) without delay.

Each vial and syringe should only be used for the treatment of a single eye.

4.3 CONTRAINDICATIONS

Ocular or Periocular Infections.

Active Intraocular Inflammation.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Bilateral Treatment

The safety and efficacy of IZERVAY administered in both eyes concurrently have not been studied in clinical trials. No data are available.

Endophthalmitis and Retinal Detachment

Intravitreal injections have been associated with endophthalmitis and retinal detachment. Proper aseptic injection techniques must always be used when administering IZERVAY. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

Increase in Intraocular Pressure

Acute increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY (see section 4.8 Adverse effects (undesirable effects)). They may occur within minutes of injection and are generally transient.

Prior to and after the intravitreal injection, patients should be assessed for elevated intraocular pressure (IOP), for example using tonometry. If necessary, ocular hypotensive medication may be given to lower the IOP. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

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

In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularisation (see section 4.8 Adverse effects (undesirable effects)). Patients with neovascular (wet) AMD in the fellow eye are at increased risk of developing the condition in the treated eye.

Patients that are receiving IZERVAY should be monitored appropriately (e.g. with optical coherence tomography (OCT) and/or fluorescein angiography). Patients should be instructed to report any relevant symptoms.

If neovascular (wet) AMD or choroidal neovascularisation develops, treatment with an appropriate anti-Vascular Endothelial Growth Factor (anti-VEGF) agent should be considered (see Section 5.1 Pharmacodynamic properties – Clinical Trials). The decision whether to continue IZERVAY and/or whether to initiate anti-VEGF treatment, should be made by the treating ophthalmologist based on clinical judgment.

Use in renal impairment

No specific studies have been conducted in patients with renal impairment. However, differences in the systemic pharmacokinetics of avacincaptad pegol were not observed based on creatinine clearance in patients with mild, moderate, or severe renal impairment; therefore, a dose adjustment is not required for use of IZERVAY in patients with renal impairment.

Use in hepatic impairment

No specific studies in patients with hepatic impairment have been conducted with avacincaptad pegol. The effect of any degree of hepatic impairment on the pharmacokinetics of IZERVAY is unknown. No dose adjustment is recommended.

Use in the elderly

Of the total number of patients who received IZERVAY in the two pivotal clinical trials (GATHER1 and GATHER2), 90% (263/292) were ≥65 years and 61% (178/292) were ≥75 years of age. No significant differences in efficacy or safety of avacincaptad pegol were seen with increasing age in these studies. No dose adjustment is required on the basis of age.

Paediatric use

The safety and efficacy of IZERVAY in paediatric patients have not been established.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinical pharmacokinetic (PK) interaction studies have been performed. *In vitro* studies indicated that avacincaptad pegol has a low potential to inhibit cytochrome P450 isozymes.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No reproductive or fertility studies have been conducted.

Use in pregnancy – Pregnancy Category B2

There are no adequate and well-controlled studies of avacincaptad pegol administration in pregnant women. The systemic exposure to avacincaptad pegol is low after ocular administration.

Avacincaptad pegol should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus.

Daily IV bolus administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in an increase in the incidence of non-adverse fetal skeletal variations: short thoracolumbar (ossification site without distal cartilage) supernumerary ribs in rats at all doses (≥0.1 mg/kg/day) and an increased incidence of full thoracolumbar supernumerary ribs in rabbits at 1.2 mg/kg/day. The clinical relevance of these findings is unknown. Plasma exposures at the lowest tested dose in rats and the no observed effect level in rabbits (0.4 mg/kg/day) were 1.2 and 2.3, respectively, based on AUC.

Use in lactation

Adverse reactions in the breastfed child cannot be excluded. There is no information regarding the presence of avacincaptad pegol in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for avacincaptad pegol and any potential adverse effects on the breastfed child from avacincaptad pegol.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

IZERVAY has a minor influence on the ability to drive and use machines. Temporary visual disturbances and blurring may occur following the intravitreal injection and the associated eye examination. Patients should not drive or use machinery until visual function has recovered sufficiently.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of avacincaptad pegol was evaluated in two sham-controlled studies in patients with GA secondary to AMD (i.e., the 18-month GATHER1 study and the 24-month GATHER2 study). A total of 624 patients constituted the safety population in these studies. Among those, 292 patients were treated with the recommended dose of 2 mg avacincaptad pegol (0.1 mL of 20 mg/mL solution). Three hundred thirty two (332) patients were assigned to sham.

The summary of treatment exposure to avacincaptad pegol in patients that were assigned to receive it in the GATHER 1 and GATHER2 studies is shown in Table 1.

Table1: Summary of Treatment Exposure to Avacincaptad Pegol in GATHER1 and GATHER2

Number of IZERVAY injections received per patient	
Mean (SD)	17.0 (6.01)
Treatment duration (in days)[1]	
Mean (SD)	597.6 (209.44)
Total exposure (patient years)	477.8

SD: Standard Deviation.

[1] Treatment duration (in days) is defined as (Last injection – First injection +30).

An ocular adverse event was observed in 62.7% of patients treated with IZERVAY and 45.8% of patients assigned to sham. A non-ocular adverse event was observed in 72.9% of patients treated with IZERVAY and 68.1% of patients assigned to sham. A serious adverse event was observed in 24.7% of patients treated with IZERVAY vs. 23.8% of patients assigned to sham. The rate of discontinuation due to an adverse event was 4.5% in patients treated with IZERVAY and 3.3% in patients assigned to sham.

Table2 summarises adverse reactions in the study eye that were observed in patients treated with IZERVAY 2 mg or Sham pooled across the two studies.

The adverse reactions reported in clinical studies are listed according to the MedDRA preferred terms 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). Within each System Organ Class (SOC), adverse reactions are presented in order of decreasing frequency.

Table 2: Study Eye Ocular Adverse Reactions Reported in Randomised, Sham-controlled Trials (GATHER1 and GATHER2)

Adverse Reaction	Frequency (%) IZERVAY 2 mg N=292	Sham N=332	Frequency category
Eye disorders			
Conjunctival haemorrhage	16.8%	9.9%	Very Common
Choroidal neovascularisation	11.6%	6.9%	Very Common
Punctate keratitis	8.2%	7.2%	Common
Eye pain	5.8%	3.3%	Common
Visual impairment	3.4%	1.5%	Common
Vision blurred	3.1%	1.2%	Common
Retinal haemorrhage	3.1%	2.7%	Common
Vitreous floaters	3.1%	1.2%	Common
Ocular hypertension	2.7%	0%	Common
Blepharitis	2.4%	0.6%	Common
Visual acuity reduced transiently	2.1%	0.6%	Common
Blindness transient	2.1%	0%	Common
Keratitis	1.4%	0.6%	Common
Photopsia	1.0%	0%	Common
Optic ischaemic neuropathy	0.3%	0%	Uncommon
Vitreal cells	0.3%	0%	Uncommon
Vitreous haemorrhage	0.3%	0%	Uncommon
Vitritis	0.3%	0%	Uncommon
Investigations			
IOP increased	12.3%	0.9%	Very Common
Injury, poisoning and procedural complications			
Corneal abrasion	2.1%	1.2%	Common
Infections and infestations			
Endophthalmitis	0.3%	0%	Uncommon

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

Neovascular (wet) AMD was observed in 11.6% of patients treated with IZERVAY and 6.9% of patients that received sham. 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 (see section 4.4 Special Warnings and Precautions for Use).

Increase in intraocular pressure

Increase in intraocular pressure was observed in 12.3% of patients treated with IZERVAY and in 0.9% of patients that received sham. The event of IOP increased was transient in nature, and none were serious. As part of clinical practice, active monitoring of IOP increased before and after the intravitreal injection and the perfusion of the optic nerve head is suggested. IOP lowering, e.g. with ocular hypertension medication, may be recommended at the discretion of the ophthalmologist (see section 4.4 Special Warnings and Precautions for Use).

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

Overdosing with greater than recommended injection volume may increase IOP. In the event of overdose, IOP should be monitored and, if deemed necessary by the treating ophthalmologist, appropriate treatment should be initiated.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Ophthalmologicals; ATC code: S01XA32.

Increased GA area growth is reflective of loss of photoreceptors and AMD disease progression. Reductions in GA growth were observed from baseline through the first year of treatment across all avacincaptad pegol treatment groups in studies GATHER1 and GATHER2.

Mechanism of action

Avacincaptad pegol is an RNA aptamer, a PEGylated oligonucleotide that binds to and inhibits complement protein C5. By inhibiting C5, avacincaptad pegol prevents its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the membrane attack complex [MAC or C5b-9]) thus preventing MAC formation. Avacincaptad pegol preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.

Clinical trials

The efficacy and safety of IZERVAY were demonstrated in two randomised, multi-centre, double-masked, sham-controlled, 18- and 24-month studies (Phase II/III trial GATHER1, and pivotal Phase III trial GATHER2, respectively) in female or male adult patients aged 50 years or over with non-foveal geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD).

Across the two trials, 292 patients were treated with avacincaptad pegol 2 mg, and 332 patients received sham. Patient ages ranged from 51 to 97 years with a mean of 77 years. Approximately 70% were female and 87% were White. Approximately 95% had bilateral GA, but both trials only treated one study eye.

In both trials, patients had no previous treatment for AMD or any prior intravitreal treatment for any indication. Patients with choroidal neovascularisation (CNV), intraocular inflammation, diabetic retinopathy, or GA secondary to any condition other than AMD were excluded.

In GATHER1, patients with suspected CNV were withdrawn from the study. In GATHER2, patients that developed CNV were concomitantly treated with anti-VEGF therapy.

In GATHER1, patients were treated with either avacincaptad pegol or sham monthly for 18 months. In GATHER2, patients were treated with avacincaptad pegol or sham monthly for the first 12 months. Patients receiving monthly avacincaptad pegol were re-randomised at Month 12 to receive either avacincaptad pegol monthly (EM) or every other month (EOM). Patients who were treated with sham in the first 12 months continued monthly sham treatment. Bilateral treatment (treatment in both eyes concurrently) was not studied.

In both trials, the primary efficacy endpoint was based on GA area measured by fundus autofluorescence (FAF) at 3 timepoints: baseline, Month 6, and Month 12 (square root transformation). Additionally, for the Year 2 analysis in GATHER2, the rate of GA growth (slope) was estimated based on GA area measured at 5 time points: baseline, Month 6, Month 12, Month 18, and Month 24.

GA area

In GATHER1, a statistically significant reduction of the least-squares mean change in GA area (square root transformed) from baseline was demonstrated for avacincaptad pegol 2 mg compared to sham at Month 12 (0.110 mm, 95% CI 0.030 to 0.190) and Month 18 (0.168 mm, 95% CI 0.066 to 0.271) (Table 3).

In GATHER2, a statistically significant reduction of the least-squares mean change in GA area (square root transformed) from baseline was demonstrated for avacincaptad pegol 2 mg compared to sham at Month 12 (0.059 mm, 95% CI 0.017 to 0.100) (Table 3). Month 24 results were analysed using GA growth rate.

Table 3: Month 12 results: Least-squares mean change in GA area (square root transformed) from GATHER1 and GATHER2.

Efficacy Endpoint (MMRM Analysis)	**GATHER1**		**GATHER2**	
	IZERVAY 2 mg N=67	**Sham N=110**	**IZERVAY 2 mg N=225**	**Sham N=222**
Mean Change in GA Area[a] (mm)	0.292	0.402	0.333	0.392
Difference vs. Sham (95% CI) (mm/year)	0.110 (0.030-0.190)		0.059 (0.017-0.100)	

Efficacy Endpoint (MMRM Analysis)	GATHER1		GATHER2	
	IZERVAY 2 mg N=67	Sham N=110	IZERVAY 2 mg N=225	Sham N=222
p value	0.0072		0.0056 [b]	

CI = Confidence Interval; GA = Geographic Atrophy; MMRM = Mixed Models for Repeated Measures.

[a] = Square root transformed.

[b] = Nominal p-value; not formally tested for statistical significance due to pre-specified testing procedure.

GA growth rate

In GATHER2, the treatment effect up to Month 24 in GA area was tested using the annualised rate of GA growth. Over the first 12 months, there was a statistically significant reduction of mean rate of GA growth (0.056 mm/year, 95% CI 0.016 to 0.096, square root transformed) in patients treated with avacincaptad pegol 2 mg compared to sham. The observed results at Month 12 are shown in Table 4 (non-square root transformed data shown), as well as in Figures 1 and 2.

12-month non-transformed GA growth data from GATHER1 are shown in Table 4 and Figure 1, noting that the pre-specified primary analysis for GATHER1 used the square root transformed GA area.

Table 4: Efficacy Outcomes at Month 12 in GATHER1 and GATHER2 Studies

Efficacy Endpoint (MMRM Analysis)	GATHER1		GATHER2	
	IZERVAY 2 mg N=67	Sham N=110	IZERVAY 2 mg N=225	Sham N=222
GA growth rate (mm^2/year) (observed)[a]	1.22	1.89	1.75	2.12
Difference vs Sham (95% CI) (mm^2/year) % Difference[b] p value[c]	0.67 (0.21-1.13) 35% 0.005		0.38 (0.12-0.63) 18% 0.004	

CI = Confidence Interval; GA = Geographic Atrophy; MMRM = Mixed Models for Repeated Measures.

[a] = Non-transformed GA growth slope analysis.

[b] = % difference is calculated by 100×(difference)/ GA growth rate in Sham.

[c] = Nominal p-values; not formally tested for statistical significance due to pre-specified testing procedure. Formal statistical testing was based on square root transformed data.

Over the 24-month study period in GATHER2, there was a reduction of the rate of GA growth in patients treated with avacincaptad pegol 2 mg (EM or EOM) compared to sham: In the EM group, the GA area growth rate difference compared to sham was 0.362 mm^2/year (95% CI 0.066 to 0.657); in the EOM group, the difference was 0.488 mm^2/year (95% CI 0.189 to 0.788) (Table 5 and Figure 2).

Table 5: Efficacy Outcomes at Month 24 in GATHER2

Efficacy Endpoint (MMRM Analysis)	GATHER2 Year 2		
	IZERVAY 2 mg EM N=96	IZERVAY 2 mg EOM N=93	Sham N=203
GA Rate of Growth (mm^2/year) (observed)[a]	2.23	2.10	2.59
Difference (95% CI) (mm^2/year) % Difference[b] p value	0.362 (0.066-0.657) 14% 0.0165	0.488 (0.189-0.788) 19% 0.0015[c]	N/A

CI = Confidence Interval; GA = Geographic Atrophy; MMRM = Mixed Models for Repeated Measures.
EM: IZERVAY monthly in year 1 and year 2.
EOM: IZERVAY monthly in year 1, every other month in year 2.
[a] = Non-transformed GA growth slope analysis.
[b] = % difference is calculated by 100×(difference)/(least square mean from Sham).
[c] = Nominal p- value; not formally tested for statistical significance due to pre-specified testing procedure.

Figure 1: Mean Change in GA Area (mm^2) From Baseline to Month 18 in GATHER1

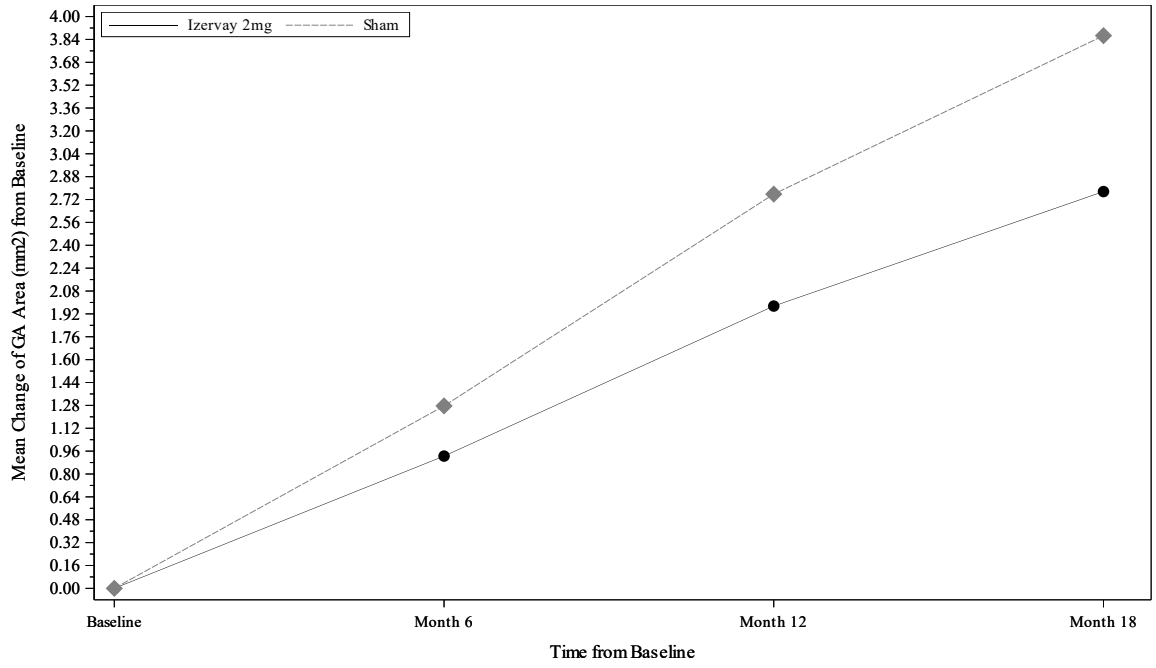
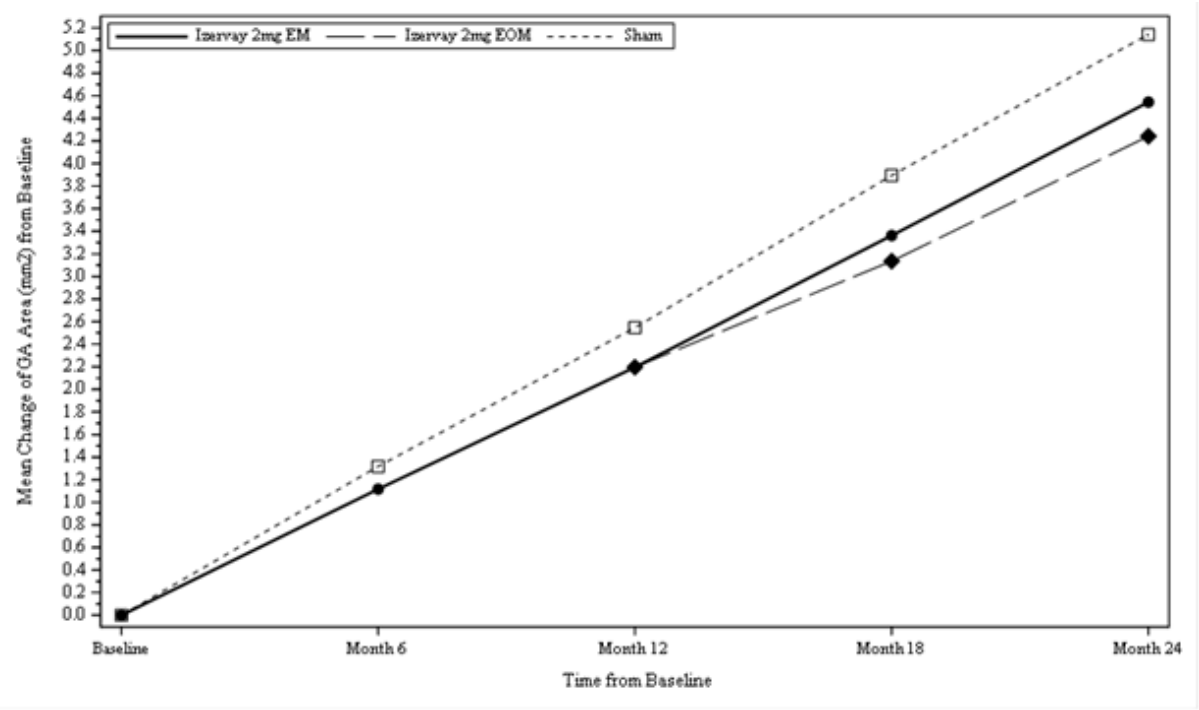


Figure 2: Mean Change in GA Area (mm^2) From Baseline GATHER2



All patients were dosed monthly from baseline to Month 12.
EM: every month
EOM: every other month

The treatment effects in the pre-specified subgroups (e.g., age, sex, baseline GA disc area) were generally consistent with the results in the overall study population.

No statistically significant treatment effect in change from baseline to Month 24 in best-corrected visual acuity (BCVA), low luminance best-corrected visual acuity (LL BCVA), or National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) overall composite score was demonstrated for avacincaptad pegol 2 mg compared to sham.

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

Steady-state maximum avacincaptad pegol plasma concentrations (C_{max}) are estimated to occur approximately 3 days post-dose. Geometric mean (GeoCV%) avacincaptad pegol plasma C_{max} is estimated to be 347 ng/mL (59.0%) at steady-state in GA secondary to AMD patients. The $AUC_{0-\tau}$ days following monthly dosing is 4726 day·ng/mL, where tau is 28 days. The mean accumulation ratio of avacincaptad pegol upon every month dosing based on C_{trough} was 1.09.

Distribution

The distribution in the vitreous humor is assumed to be homogenous with a volume of 4 mL. The concentration of avacincaptad pegol in the vitreous humor after dosing with 2 mg dose are 500,000 ng/mL (2,000 µg/4 mL). Given an observed C_{max} of 347 ng/mL, the systemic exposure is predicted to be 1,400 times lower than exposure in the vitreous humor.

Metabolism

Metabolism of avacincaptad pegol has not been fully characterised. Avacincaptad pegol is expected to be catabolised by endonucleases and exonucleases to oligonucleotides of shorter lengths.

Excretion

Elimination of avacincaptad pegol has not been fully characterised. Avacincaptad pegol was not detected in human urine. The estimated mean apparent systemic half-life of avacincaptad pegol is 8 days.

Pharmacokinetic Characteristics in Special Populations

Following repeat monthly intravitreal dose administration of 2 mg avacincaptad pegol, no differences in the systemic pharmacokinetics of avacincaptad pegol were observed based on age, sex, and body weight. No special dosage modification is required for any of the populations that have been studied (e.g., age, sex, and body weight). There were no differences observed in the systemic pharmacokinetics of avacincaptad pegol based on creatinine clearance in patients with mild, moderate, or severe renal impairment. No dosage adjustment is needed based on renal impairment status. The effect that any degree of hepatic impairment has on the pharmacokinetics of avacincaptad pegol is unknown. As significant increases in plasma IZERVAY exposures are not expected with an intravitreal route of administration, no dosage adjustment is needed based on hepatic impairment status.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Avacincaptad pegol was negative in the bacterial reverse mutation (Ames) assay, an *in vitro* mammalian chromosome aberration assay using human lymphocytes and in an *in vivo* mouse bone marrow micronucleus assay.

Carcinogenicity

No studies have been conducted on the carcinogenic potential of avacincaptad pegol.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Dibasic sodium phosphate heptahydrate
Monobasic sodium phosphate monohydrate
Sodium chloride
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 in a refrigerator between 2°C and 8°C. Do not freeze.

Prior to use, the unopened glass vial of avacincaptad pegol may be kept at room temperature, 15°C to 25°C for up to 24 hours.

Store the vial in the original carton to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Type 1 clear glass vial with a coated rubber stopper sealed with an aluminium seal with a white plastic flip-off cap.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

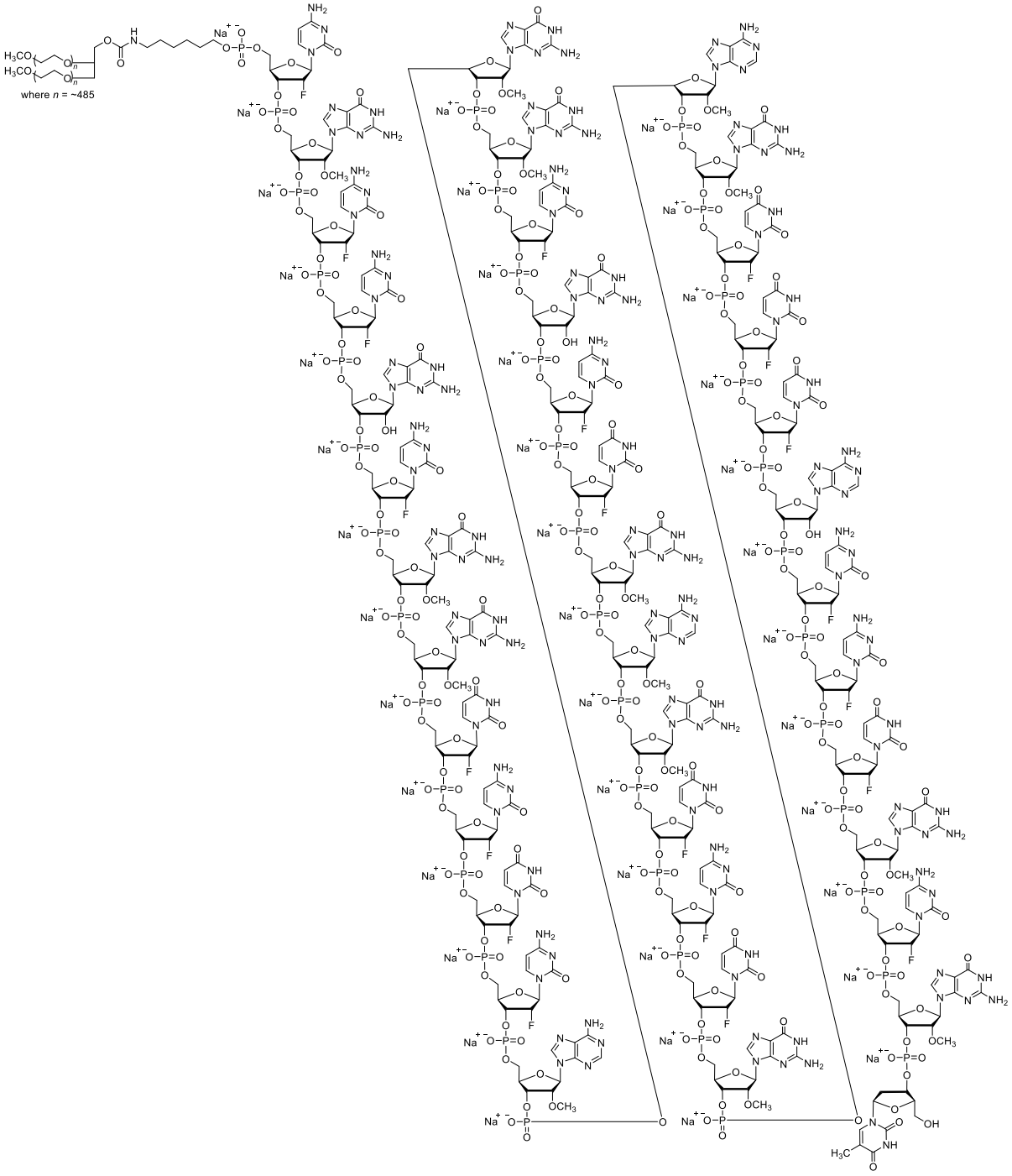
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

IZERVAY contains avacincaptad pegol sodium, a complement C5 inhibitor. Avacincaptad pegol is a ribonucleic acid (RNA) aptamer, covalently bound to an approximately 43-kiloDalton (kDa) branched polyethylene glycol (PEG) molecule.

The molecular formula of avacincaptad pegol (free acid form) is $C_{395}H_{492}N_{142}O_{262}P_{39}F_{21}((CH_2)_2O)_n$ where n~970 and the molecular weight is approximately 56 kDa. The structure of avacincaptad pegol sodium is presented below.

Chemical structure



CAS number

1491144-00-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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Website: www.astellas.com/au

9 DATE OF FIRST APPROVAL

13 October 2025

10 DATE OF REVISION

10 June 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Change the temperature range that the unopened glass vial may be kept at for up to 24 hours before use
6.4	Change the temperature range that the unopened glass vial may be kept at for up to 24 hours before use