HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ENZEEVU safely and effectively. See full prescribing information for ENZEEVU.

ENZEEVU™ (aflibercept-abzv) injection, for intravitreal use
Initial U.S. Approval: 2024
ENZEEVU (aflibercept-abzv) is biosimilar* to EYLEA® (aflibercept).

----------INDICATIONS AND USAGE----------
ENZEEVU is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:
- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)

----------DOSAGE AND ADMINISTRATION----------
- **Neovascular (Wet) Age-Related Macular Degeneration (AMD)**
  - The recommended dose for ENZEEVU is 2 mg (0.05 mL of 40 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL of 40 mg/mL solution) via intravitreal injection once every 8 weeks (2 months). (2.2)
  - Although ENZEEVU may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). (2.2)
  - Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Injection: 2 mg (0.05 mL of 40 mg/mL) solution in a single-dose pre-filled syringe (3)
- Injection: 2 mg (0.05 mL of 40 mg/mL) solution in a single-dose vial (3)

----------CONTRAINDICATIONS----------
- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis, retinal detachments, and retinal vasculitis with or without occlusion may occur following intravitreal injections. Patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis, retinal detachment, or retinal vasculitis without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥5%) reported in patients receiving aflibercept were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

* Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of ENZEEVU has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 8/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ENZEEVU is indicated for the treatment of:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions

For ophthalmic intravitreal injection. ENZEEVU must only be administered by a qualified physician.

Pre-filled Syringe: A 30-gauge x ½ inch sterile injection needle is needed but not provided.

Vial: A sterile 5-micron blunt filter needle (18-gauge x 1½ inch), a sterile 1 mL syringe with a 0.05 mL dose mark, and a sterile 30-gauge x ½ inch injection needle are needed and are supplied with the vial.

ENZEEVU is available packaged as follows:

- Pre-filled Syringe. The ENZEEVU syringe stopper and tip cap are not made with natural rubber latex.
- Vial Kit with Injection Components (filter needle, syringe, injection needle). The ENZEEVU vial stopper and the stopper of supplied syringe are not made with natural rubber latex.

  [see How Supplied/Storage and Handling (16)].

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The recommended dose for ENZEEVU is 2 mg (0.05 mL of 40 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL of 40 mg/mL solution) via intravitreal injection once every 8 weeks (2 months). Although ENZEEVU may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks *[see Clinical Studies (14.1)]*. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.

2.3 Preparation for Administration – Pre-filled Syringe

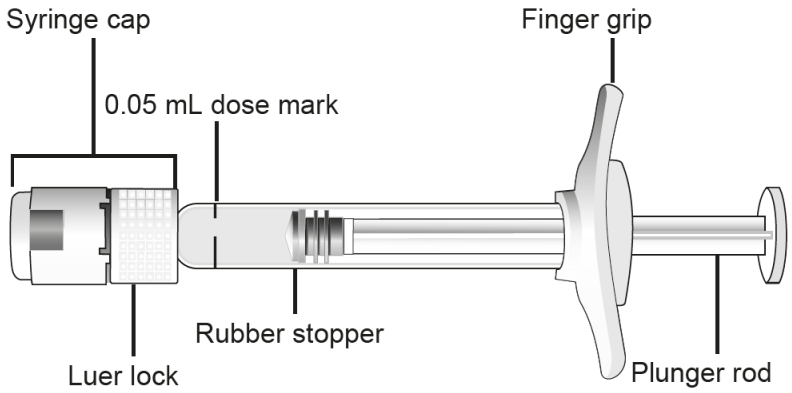
The ENZEEVU pre-filled glass syringe is sterile and for one-time use in one eye only.

The pre-filled syringe should be inspected visually prior to administration. **Do not** use if particulates, cloudiness and/or discoloration are visible, or if the package is open or damaged. **Do not** use if any part of the pre-filled syringe is damaged or if the syringe cap is detached from the Luer lock.

The intravitreal injection should be performed with a 30-gauge x ½ inch injection needle (not provided).

The pre-filled syringe contains more than the recommended dose of 2 mg aflibercept-abzv (equivalent to 50 microliters). **The excess volume must be discarded prior to the administration.**

Pre-filled Syringe Description – Figure 1



Use aseptic technique to carry out the following steps:

1 When ready to administer ENZEEVU, open the carton and remove sterilized blister pack. Carefully peel open the sterilized blister pack ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.

2 Using aseptic technique, remove the syringe from the sterilized blister pack.

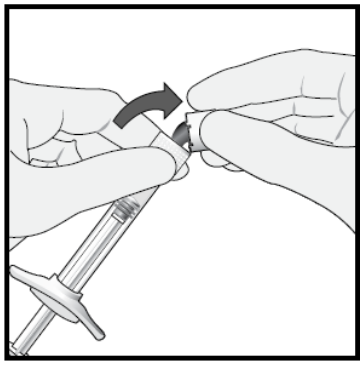
3 SNAP OFF SYRINGE CAP

To remove the syringe cap, hold the syringe in one hand while using the other hand to grasp the syringe cap with the thumb and forefinger.

Snap off (do not turn or twist) the syringe cap (see Figure 2).

Note: To avoid compromising the sterility of the product, do not pull back on the plunger.

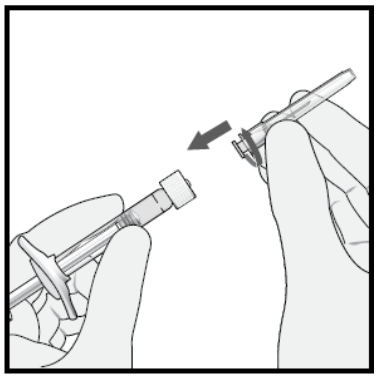
Figure 2



4 Using aseptic technique, firmly twist a 30-gauge x ½ inch injection needle onto the Luer lock syringe tip (see Figure 3).

Note: When ready to administer ENZEEVU, carefully remove the needle cap by pulling it straight off.

Figure 3



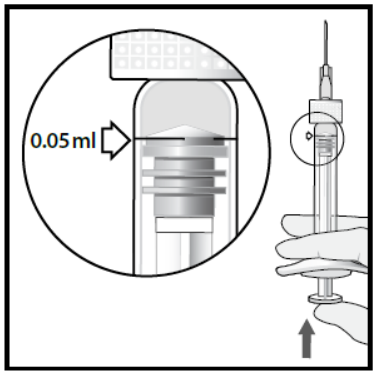
5 Holding the syringe with the needle pointing up, check the syringe for bubbles.

If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 4).

Figure 4

6 To eliminate all bubbles and expel excess drug, slowly depress the plunger rod to align the plunger dome edge with the black dosing line on the syringe (equivalent to 50 microliters) (see Figure 5).

Figure 5



7 The pre-filled syringe is for one-time use in one eye only. After injection any unused product must be discarded.

2.4 Preparation for Administration – Vial

ENZEEVU should be inspected visually prior to administration. If particulates, cloudiness and/or discoloration are visible, the vial must not be used.

The glass vial is for one-time use in one eye only.

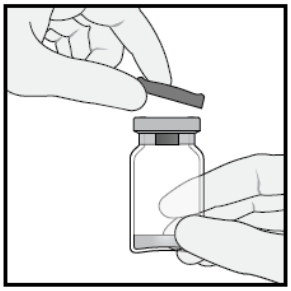
Use aseptic technique to carry out the following preparation steps:

Prepare for intravitreal injection with the following medical devices for single use:

- A 5-micron blunt filter needle (18-gauge x 1½ inch), sterile, supplied with the vial
- A 1 mL syringe with a 0.05 mL dose mark, sterile, supplied with the vial
- A 30-gauge x ½ inch injection needle, sterile, supplied with the vial.

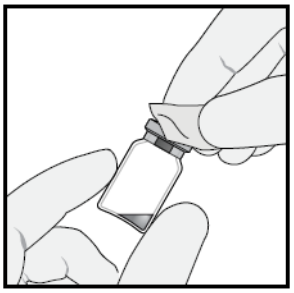
1 Remove the protective plastic cap from the vial (see Figure 6).

Figure 6



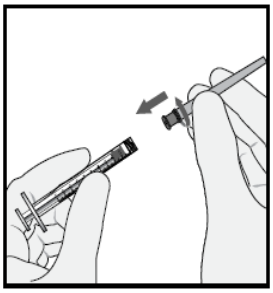
2 Clean the top of the vial with an alcohol wipe (see Figure 7).

Figure 7



3 Remove the 18-gauge x 1½-inch, 5-micron, filter needle and the 1-mL syringe from their packaging. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see Figure 8).

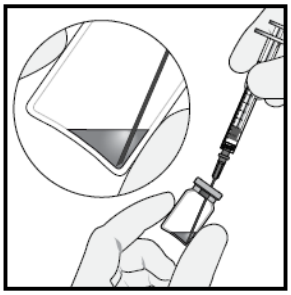
Figure 8



4 Push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.

5 Using aseptic technique withdraw all of the ENZEEVU vial content into the syringe, keeping the vial in an upright position, **slightly inclined to ease complete withdrawal**. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid (see Figure 9).

Figure 9



6 Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

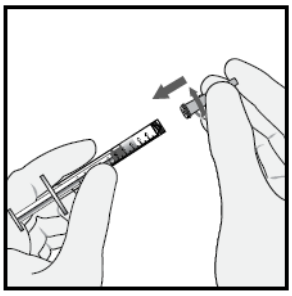
7 Remove the filter needle from the syringe and properly dispose of the filter needle.

Note: Filter needle is **not** to be used for intravitreal injection.

8 Remove the 30-gauge x ½-inch injection needle from its packaging and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 10).

When ready to administer ENZEEVU, carefully remove the needle cap by pulling it straight off.

Figure 10

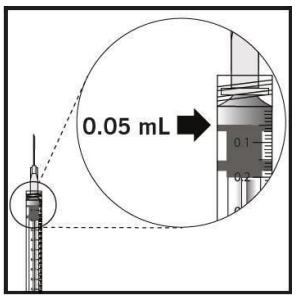


9 Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 11).

Figure 11

10 To eliminate all of the bubbles and to expel excess drug, **slowly** depress the plunger so that the plunger tip aligns with the line that marks **0.05 mL** on the syringe (see Figure 12).

Figure 12



11 The vial is for one-time use in one eye only. After injection any unused product must be discarded.

2.5 Injection Procedure

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Pre-filled Syringe: Inject by pressing the plunger carefully and with constant pressure. Do not apply additional pressure once the plunger has reached the bottom of the syringe. A small residual volume may remain in the syringe after a full dose has been injected. This is normal. **Do not administer any residual solution observed in the syringe.**

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. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay *[see Patient Counseling Information (17)]*.

Each sterile, pre-filled syringe or vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new sterile, pre-filled syringe or vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before ENZEEVU is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

ENZEEVU is a clear, colorless to slightly brownish-yellow solution available as:

- Injection: 2 mg (0.05 mL of a 40 mg/mL solution) in a single-dose pre-filled glass syringe
- Injection: 2 mg (0.05 mL of a 40 mg/mL solution) in a single-dose glass vial

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

ENZEEVU is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

ENZEEVU is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

ENZEEVU is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in ENZEEVU. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis, Retinal Detachments, and Retinal Vasculitis with or without Occlusion

Intravitreal injections, including those with aflibercept products, have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]* and, more rarely, retinal vasculitis with or without occlusion *[see Adverse Reactions (6.2)]*. Proper aseptic injection technique must always be used when administering ENZEEVU. Patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis, retinal detachment, or retinal vasculitis without delay and should be managed appropriately *[see Dosage and Administration (2.5) and Patient Counseling Information (17)]*.

5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with aflibercept products *[see Adverse Reactions (6.1)]*. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately *[see Dosage and Administration (2.5)]*.

5.3 Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including aflibercept products. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with aflibercept compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the aflibercept group compared with 3.2% (19 out of 595) in the ranibizumab group.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4.3)]*
- Endophthalmitis, Retinal detachments and Retinal Vasculitis with or without Occlusion *[see Warnings and Precautions (5.1)]*
- Increase in intraocular pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic events *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2980 adult patients treated with aflibercept constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with aflibercept including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving aflibercept were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The data described below reflect exposure to aflibercept in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1) *[see Clinical Studies (14.1)]*.

Safety data observed in the aflibercept group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 96	
	Aflibercept (N=1824)	Active Control (ranibizumab) (N=595)	Aflibercept (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with aflibercept were hypersensitivity, retinal tear, and endophthalmitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of aflibercept. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye disorders: retinal vasculitis and occlusive retinal vasculitis related to intravitreal injection with aflibercept (reported at a rate of 0.6 and 0.2 per 1 million injections, respectively, based on postmarketing experience from November 2011 until November 2023).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with aflibercept have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose *[see Animal Data]*.

Animal reproduction studies are not always predictive of human response, and it is not known whether aflibercept can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept *[see Clinical Pharmacology (12.1)]*, treatment with aflibercept may pose a risk to human embryofetal development. ENZEEVU should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in adult patients after a single intravitreal dose of 2 mg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of aflibercept products in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, ENZEEVU is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENZEEVU and any potential adverse effects on the breastfed child from ENZEEVU.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of ENZEEVU.

Infertility

There are no data regarding the effects of aflibercept on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed in adult patients with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

A pediatric assessment for ENZEEVU demonstrates that ENZEEVU is safe and effective for pediatric patients in an indication for which EYLEA (aflibercept) is approved. However, ENZEEVU is not approved for such indication due to marketing exclusivity for EYLEA (aflibercept).

8.5 Geriatric Use

In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with aflibercept were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

10 OVERDOSAGE

Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdosage, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

11 DESCRIPTION

Aflibercept-abzv is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept-abzv is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept-abzv is produced in recombinant Chinese hamster ovary (CHO) cells.

ENZEEVU (aflibercept-abzv) injection is a sterile, clear, and colorless to slightly brownish-yellow solution. ENZEEVU does not contain anti-microbial preservative and is supplied as a sterile, aqueous solution for intravitreal injection in a single-dose pre-filled glass syringe or a single-dose glass vial designed to deliver 0.05 mL (50 microliters) of solution containing 2 mg of aflibercept-abzv in histidine (0.023 mg), L-histidine hydrochloride monohydrate (0.073 mg), polysorbate 20 (0.02 mg), trehalose (3.6 mg) with a pH of 5.7. Hydrochloric acid and sodium hydroxide may be added to adjust the pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability.

Aflibercept products act as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

12.2 Pharmacodynamics

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

In the clinical studies anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52. Anatomic data were not used to influence treatment decisions during the first year.

12.3 Pharmacokinetics

Aflibercept is administered intravitreally to exert local effects in the eye. In patients with wet AMD, following intravitreal administration of aflibercept, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept:VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept:VEGF complex).

Absorption/Distribution

Following intravitreal administration of 2 mg per eye of aflibercept to patients with wet AMD, the mean C_{max} of free aflibercept in the plasma was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL) and was attained in 1 to 3 days. The free

aflibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeated doses intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100 fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

The volume of distribution of free aflibercept following intravenous (I.V.) administration of aflibercept has been determined to be approximately 6L.

Metabolism/Elimination
Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The terminal elimination half-life (t1/2) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.

Specific Populations

Renal Impairment
Pharmacokinetic analysis of a subgroup of patients (n=492) in one wet AMD study, of which 43% had renal impairment (mild n=120, moderate n=74, and severe n=16), revealed no differences with respect to plasma concentrations of free aflibercept after intravitreal administration every 4 or 8 weeks. No dose adjustment based on renal impairment status is needed for wet AMD patients.

Other
No dosage modification is required based on gender or in the elderly.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of aflibercept or of other aflibercept products.

In the wet AMD and other indications studies, the pre-treatment incidence of immunoreactivity to aflibercept was approximately 1% to 3% across treatment groups. After dosing with aflibercept for 24-100 weeks, antibodies to aflibercept were detected in a similar percentage range of patients.

There were no differences in efficacy or safety between patients with or without immunoreactivity.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept products. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at weekly doses ranging from 3 to 30 mg per kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. A No Observed Adverse Effect Level (NOAEL) was not identified. Intravenous administration of the lowest dose of aflibercept assessed in monkeys (3 mg per kg) resulted in systemic exposure (AUC) for free aflibercept that was approximately 1500 times higher than the systemic exposure observed in adult patients after an intravitreal dose of 2 mg. All changes were reversible within 20 weeks after cessation of treatment.

13.2 Animal Toxicology and/or Pharmacology

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2 or 4 mg per eye. At the NOAEL of 0.5 mg per eye in monkeys, the systemic exposure (AUC) was 56 times higher than the exposure observed in adult patients after an intravitreal dose of 2 mg. Similar effects were not seen in other clinical studies *[see Clinical Studies (14)]*.

14 CLINICAL STUDIES

14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) Aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) Aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) Aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). Protocol-specified visits occurred every 28±3 days. Patient ages ranged from 49 to 99 years with a mean of 76 years.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Both aflibercept 2Q8 and aflibercept 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1.

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 2 and Figure 12 below.

Table 2: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies

	VIEW1			VIEW2		
	Aflibercept 2 mg Q8 weeks [a]	Aflibercept 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks	Aflibercept 2 mg Q8 weeks [a]	Aflibercept 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
Efficacy Outcomes						
Proportion of patients who maintained visual acuity (%) (<15 letters of BCVA loss)	94%	95%	94%	95%	95%	95%
Difference[b] (%) (95.1% CI)	0.6 (-3.2, 4.4)	1.3 (-2.4, 5.0)		0.6 (-2.9, 4.0)	-0.3 (-4.0, 3.3)	
Mean change in BCVA as measured by ETDRS letter score from Baseline	7.9	10.9	8.1	8.9	7.6	9.4
Difference[b] in LS mean (95.1% CI)	0.3 (-2.0, 2.5)	3.2 (0.9, 5.4)		-0.9 (-3.1, 1.3)	-2.0 (-4.1, 0.2)	
Number of patients who gained at least 15 letters of vision from Baseline (%)	92 (31%)	114 (38%)	94 (31%)	96 (31%)	91 (29%)	99 (34%)
Difference[b] (%) (95.1% CI)	-0.4 (-7.7, 7.0)	6.6 (-1.0, 14.1)		-2.6 (-10.2, 4.9)	-4.6 (-12.1, 2.9)	

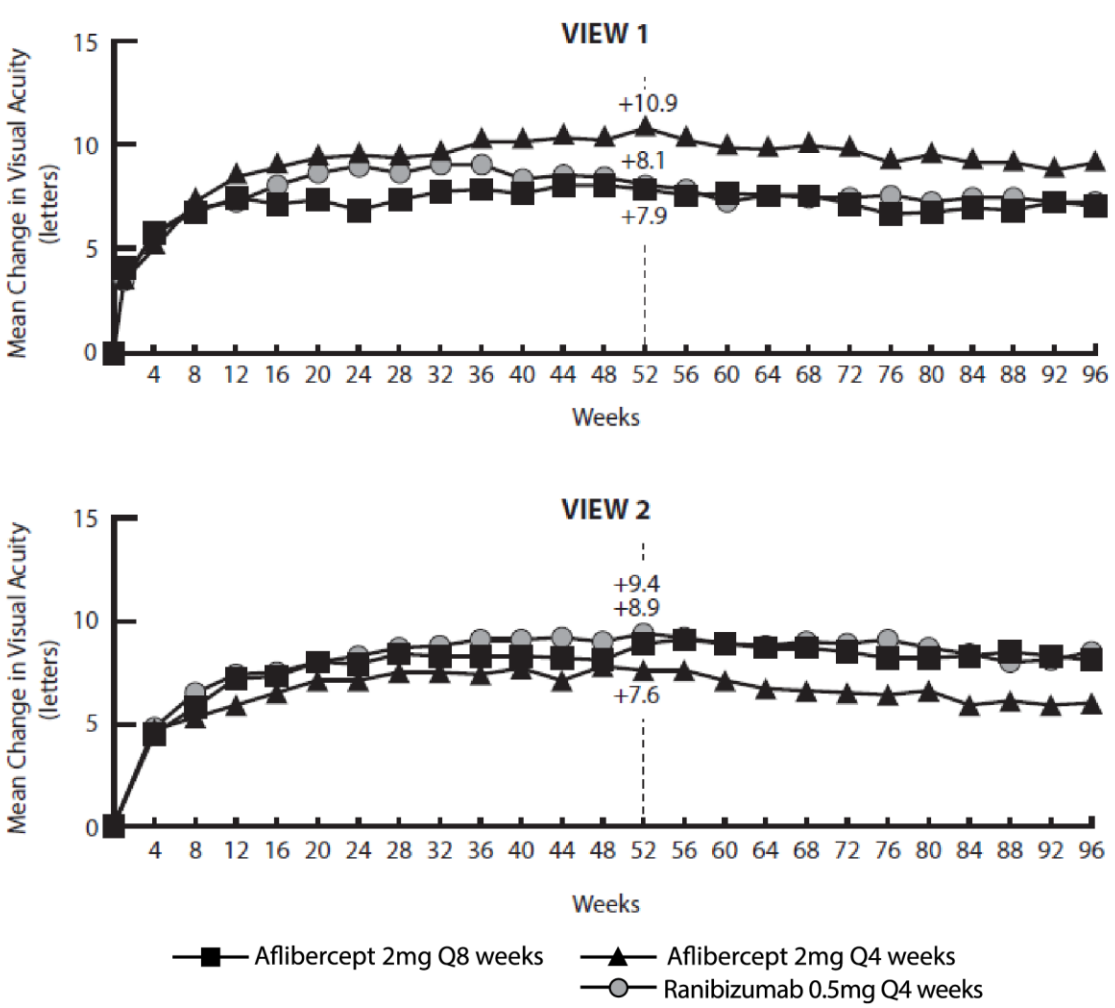
BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = Last Observation Carried Forward (baseline values are not carried forward); 95.1% confidence intervals were presented to adjust for safety assessment conducted during the study

[a] After treatment initiation with 3 monthly doses

[b] Aflibercept group minus the ranibizumab group

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity) in each study were in general consistent with the results in the overall populations.

Figure 12: Mean Change in Visual Acuity from Baseline to Week 96* in VIEW1 and VIEW2 Studies



*Patient dosing schedules were individualized from weeks 52 to 96 using a modified 12-week dosing regimen.

VIEW1 and VIEW2 studies were both 96 weeks in duration. However, after 52 weeks patients no longer followed a fixed dosing schedule. Between week 52 and week 96, patients continued to receive the drug and dosage strength to which they were initially randomized on a modified 12 week dosing schedule (doses at least every 12 weeks and additional doses as needed). Therefore, during the second year of these studies there was no active control comparison arm.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Each pre-filled syringe or vial is for single eye use only. Discard unused portion. ENZEEVU injection is a clear, colorless to slightly brownish-yellow solution and is supplied in the following presentations *[see Dosage and Administration (2.1), (2.3), (2.4) and (2.5)]*.

NDC NUMBER	CARTON TYPE	CARTON CONTENTS
61314-504-63	Pre-filled Syringe	one blister pack containing one ENZEEVU 2 mg (0.05 mL of a 40 mg/mL solution) sterile, single-dose pre-filled glass syringe one Prescribing Information
61314-504-94	Vial Kit with Injection Components	one ENZEEVU 2 mg (0.05 mL of a 40 mg/mL solution) single-dose glass vial one 5-micron blunt filter needle (18-gauge x 1½ inch), sterile, for withdrawal of the vial contents one 30-gauge x ½ inch injection needle, sterile, for intravitreal injection one 1 mL syringe with a 0.05 mL dose mark, sterile, for administration one Prescribing Information

The ENZEEVU syringe stopper and tip cap are not made with natural rubber latex.

The ENZEEVU vial stopper and the stopper of supplied syringe are not made with natural rubber latex.

16.2 Storage and Handling

Store ENZEEVU in the refrigerator at 2°C to 8ºC (36°F to 46ºF). Do not freeze. Do not use beyond the date stamped on the carton and container label. Store in the original carton until time of use to protect from light. Do not open sealed blister tray or vial until time of use. Prior to usage, the unopened blister or vial of ENZEEVU may be stored at room temperature (below 30°C/86°F) for up to 14 days.

17 PATIENT COUNSELING INFORMATION

In the days following ENZEEVU administration, patients are at risk of developing endophthalmitis, retinal detachment or retinal vasculitis with or without occlusion. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients and/or caregivers to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

Patients may experience temporary visual disturbances after an intravitreal injection with ENZEEVU and the associated eye examinations *[see Adverse Reactions (6)]*. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured by:

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Princeton, NJ 08540

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