NATIONAL PHARMACEUTICAL REGULATORY AGENCY
MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY

PRODUCT NAME:
Yesafili 40mg/mL solution for injection in a vial (MAL24126015ACZ)

ACTIVE INGREDIENT:
Aflibercept 40mg/mL

PRODUCT REGISTRATION HOLDER:
Biocon Sdn Bhd

PRODUCT MANUFACTURER:
Biocon Biologics Limited, India

APPROVAL DATE:
2 December 2024 (DCA 403)

1.0 BACKGROUND INFORMATION

- Yesafili is a biosimilar product to the reference product, Eylea (containing aflibercept, a vascular endothelial growth factor (VEGF) inhibitor) manufactured by Bayer AG, Germany.
- The DCA has not previously registered any biosimilar products containing aflibercept.
- Following the reliance and risk-based approach, the assessment focused on verification of the sameness between what has been approved by the chosen reference agency (EMA) and the dossier submitted, except for Malaysian-specific requirements, particularly the labelling for biosimilar products and risk minimization to be implemented in Malaysia.

1.1 Approved Indication

Yesafili is indicated for the treatment of

- Neovascular (wet) age-related macular degeneration (wet AMD)
- Visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- Visual impairment due to diabetic macular oedema (DME)
- Visual impairment due to myopic choroidal neovascularisation (myopic CNV)

1.2 Approved Posology

Dosage and Administration
Yesafili is for intravitreal injection.
Yesafili must only be administered by a qualified physician experienced in administering intravitreal injections.

Dosage Regimen
Neovascular (wet) age-related macular degeneration (wet AMD)
The recommended dose for Yesafili is 2 mg aflibercept, equivalent to 0.05 mL.

Yesafili treatment is initiated with one injection per month for three consecutive doses. The treatment interval is then extended to two months.

Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at two months or further extended using a treat-and-extend dosing regimen, where injection intervals are increased in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.

There is no requirement for monitoring between injections. Based on the physician's judgement the schedule of monitoring visits may be more frequent than the injection visits.

Treatment intervals greater than four months or shorter than 4 weeks between injections have not been studied.

Macular oedema secondary to RVO (branch RVO or central RVO)
The recommended dose for Yesafili is 2 mg aflibercept equivalent to 0.05 mL.

After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month.

If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Yesafili should be discontinued.

Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed.

Treatment may then be continued with a treat-and-extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.

The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response.

Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).

Diabetic macular oedema (DME)
The recommended dose for Yesafili is 2 mg aflibercept equivalent to 0.05 mL.

Yesafili treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.

After the first 12 months of treatment with Yesafili and based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be extended, such as with a treat-and-extend dosing regimen, where the treatment intervals are usually increased by 2-week increments to maintain stable visual and/or anatomic outcomes. There are limited data for treatment intervals longer than 4 months. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.

Treatment intervals shorter than 4 weeks between injections have not been studied (see section Pharmacodynamic Properties).

The schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections.

If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Yesafili should be discontinued.

Myopic choroidal neovascularisation (myopic CNV)
The recommended dose for Yesafili is a single intravitreal injection of 2 mg aflibercept equivalent to 0.05 mL.

Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease.

The schedule for monitoring should be determined by the treating physician.

The interval between two doses should not be shorter than one month.

Additional Information on Special Populations
Patients with Hepatic and/or renal impairment
No specific studies in patients with hepatic and/or renal impairment have been conducted with aflibercept.

Available data do not suggest a need for a dose adjustment with Yesafili in these patients.

Paediatric population
The safety and efficacy of aflibercept have not been established in children and adolescents. There is no relevant use of aflibercept in the paediatric population for the indications of wet AMD, CRVO, BRVO, DME and myopic CNV.

Elderly population
No special considerations are needed for dosing as phase III clinical trials were conducted in this subpopulation (see section Clinical Studies). There is limited experience in patients older than 75 years with DME.

1.3 Method of administration

Intravitreal injection

1.4 Pharmacological Aspects

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 potent 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. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes and is also known to promote leucocyte infiltration and vascular inflammation.

Pharmacokinetic Properties:

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

Absorption / Distribution

Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration and is predominately observed in the systemic circulation as an inactive, stable complex with VEGF; however only “free aflibercept” is able to bind endogenous VEGF.

In a pharmacokinetic sub-study in 6 neovascular wet AMD patients with frequent sampling, maximum plasma concentrations of free aflibercept (systemic Cmax) were low, with a mean of approximately 0.02 microgram/mL (range 0 to 0.054) within 1 to 3 days after a 2 mg intravitreal injection and were undetectable two weeks following dose in almost all patients. Aflibercept does not accumulate in the plasma when administered intravitreally every 4 weeks.

The mean maximum plasma concentration of free aflibercept is approximately 50 to 500 times below the aflibercept concentration required to inhibit the biologic activity of systemic VEGF by 50% in animal models, in which blood pressure changes were observed after circulating levels of free aflibercept attained approximately 10 microgram/mL and returned to baseline when levels fell below approximately 1 microgram/mL. 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 (2.91 microgram/mL) in a study of healthy volunteers. Therefore, systemic pharmacodynamic effects such as blood pressure changes are unlikely.

In pharmacokinetic sub-studies in patients with CRVO, BRVO, DME or myopic CNV mean Cmax of free aflibercept in plasma were similar with values in the range of 0.03 to 0.05 microgram/mL and individual values not exceeding 0.14 microgram/mL. Thereafter, plasma concentrations of free aflibercept declined to values below or close to the lower limit of quantitation generally

within one week; undetectable concentrations were reached before the next administration after 4 weeks in all patients.

Elimination
As aflibercept is a protein-based therapeutic, no metabolism studies have been conducted.

Free aflibercept binds VEGF to form a stable, inert complex. As with other large proteins, both free and bound aflibercept are expected to be cleared by proteolytic catabolism.

Renal Impairment
No special studies in patients with renal impairment have been conducted with aflibercept.

Pharmacokinetic analysis of patients in the VIEW2 study, of which 40% had renal impairment (24% mild, 15% moderate, and 1% severe), revealed no differences with respect to plasma concentrations of active substance after intravitreal administration every 4 or 8 weeks.

Similar results were seen in patients with CRVO in the GALILEO study, in patients with DME in the VIVIDDME study, and in patients with myopic CNV in the MYRROR study.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Drug Substance

- Aflibercept is a recombinant fusion protein consisting of portions of human vascular endothelial growth factor (VEGF) receptor-1 (VEGFR-1) and receptor-2 (VEGFR-2) extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG1) and is produced in recombinant Chinese Hamster Ovary (CHO) cells.
- The manufacturing process and controls has been described accordingly and considered to be satisfactory.
- The drug substance upstream and downstream processes have been validated through three consecutive 2000 L scale batches and have been demonstrated to consistently produce drug substances meeting its pre-defined acceptance criteria.
- EMA has requested for implementation of a qualitative control of the glycan profile at release of the active substance to ensure batch-to-batch consistency of the glycan profile before the first commercial scale batch is released. A commitment to do the same has been submitted for Malaysia.
- The data from the stability studies support the 36 months proposed shelf life of DS when stored at ≤ −65°C in a polycarbonate bottle with a silicone-lined polypropylene closure.
- Good Manufacturing Practice (GMP) compliance for the drug substance manufacturer (WuXi Biologics Co. Ltd, China) was issued by ANVISA, Brazil.

2.1.2 Drug Product

- The manufacturing process steps were validated using four consecutive drug product lots in the range of 11 L to 14 L (12 kg to 14.5 kg). All process validation results were within acceptance limits.
- The stability data submitted supported the proposed shelf-life of 36 months when stored at 2°C to 8°C in a type I glass vial.
- Yesafili is a clear, colourless to pale yellow solution, available in packs containing 1 vial and a 5-micron (18 G ×1½-inch) filter needle.
- The product has passed the evaluation on analytical protocol and method validation in accordance with the ICH Q2 (R1) guidelines.
- Good Manufacturing Practice (GMP) compliance for the contract manufacturer (Patheon Manufacturing Services LLC, US) was issued by Turkish Medicines and Medical Devices Agency while the GMP cert for the batch releaser (Biocon Biologics Limited, India) was issued by Health Products Regulatory Authority, Ireland.
- Medical device registration certificates for the needle had been issued by the Medical Device Authority.

2.1.3 Quality Comparability Exercise for Biosimilar Product

- Analytical data from ten drug product lots were used to execute the analytical similarity assessment of aflibercept compared to reference protein product (RPP, Eylea) sourced from US (13 lots) and EU (10 lots).
- Quality attributes of aflibercept were ranked (low, moderate, high and very high risk) based on a risk assessment that took into account potential impacts on clinical performance and the degree of uncertainty.
- The selected comprehensive set of orthogonal state-of-the–art analytical methods, which covers primary and higher order structure, size, glycoform and charge variants, post-translational modifications, protein concentration, as well as multiple biological functions mediated by the VEGF receptor domains or the Fc portion, appears adequate to address the relevant quality attributes of aflibercept.
- A comprehensive analytical biosimilarity exercise was conducted and demonstrated that, from a quality perspective, Yesafili was shown to be highly similar to the EU-Eylea and US-Eylea. Any observed analytical differences have been adequately justified and are not expected to have a relevant impact on clinical performance of the product.
- Forced degradation stability study was conducted between the biosimilar, EU-Eylea and US-Eylea to compare the degradation profile. The forced degradation conditions included freeze thaw, agitation, heat, acid, base, oxidation and fluorescent light. The degradation pathway of Yesafili was overall similar with Eylea sourced from EU and US.
- In conclusion, the data provided is consistent with EMA's evaluation and supports the biosimilarity of Yesafili compared to EU-Eylea and US-Eylea at quality level.

2.2 Non-Clinical Study Comparability for Biosimilar Product

- Primary pharmacodynamic studies include comparison of Yesafili and its comparators (EU-Eylea and US-Eylea) for the VEGF-A_{165} related activity, binding to other VEGF-A isoform (VEGFA_{121}, VEGF-A_{189}, VEGF-A_{110} and VEGF-A_{206}), binding to other VEGF isoform (VEGF-B_{167}, VEGF-C, VEGF-D) and binding to other factors (PlGF-2 binding to VEGFR1, Galectin-1).
- Secondary pharmacodynamics studies include investigation on binding to Fc region of the aflibercept (FcγRI, FcγRIIa-H131, FcγRIIa-R131, FcγRIIb, FcγRIIIa-V158, FcγRIIIb, C1q, FcRn) and Fc effector function (ADCC, CDC).
- The totality of evidence from the nonclinical primary and secondary pharmacodynamic assays demonstrate that Yesafili is similar to the reference product Eylea.
- A comparative single dose PK study provided supportive evidence of the high similarity in both systemic and ocular disposition of Yesalifi and JP-Eylea following a single IVT injection in male Dutch Belted rabbits.
- No non-clinical toxicology studies were conducted in view of a complete package of similarity data collected from a sensitive and comprehensive battery of in vitro studies, demonstrating a low risk of potential differences in non-clinical efficacy, PK, and non-immunogenicity-related general toxicity between Yesafili and Eylea reference product. As a result of low systemic exposure following the intended intravitreal route of administration, the systemic toxicity is minimal.
- In conclusion, the data provided is consistent with EMA's evaluation and supports the biosimilarity between Yesafili and Eylea reference product from a non-clinical perspective.

2.3 Clinical Study Comparability for Biosimilar Product

2.3.1 Pharmacokinetic (PK) / Efficacy

- The PK profiles of Yesafili and US-Eylea were compared in a subset of patients enrolled in clinical Phase III study (MYL-1701P-3001) to support a comparative evaluation between the two products. The overall complementary PK assessment in a subset of DME patients supports biosimilarity between Yesafili and Eylea.
- Clinical efficacy was supported by Study MYL-1701P-3001.

Table 1: Summary of Clinical Studies Conducted

Study Type & Design	Objective (s) of the Study	Treatment	Results
Study MYL-1701P-3001 Multicenter, randomized, double masked, active controlled, comparative	To demonstrate that no clinically meaningful differences exist between MYL-1701P and US-licensed Eylea	2 mg (0.05 mL) aflibercept intravitreal injection every 4 weeks for a total of 5 injections, and then	**Primary Endpoint:** Mean change from baseline in best corrected visual acuity (BCVA) as assessed by early treatment diabetic retinopathy study (ETDRS) letters at Week 8 **Prespecified equivalence margin:** Treatment difference of mean change in BCVA, from baseline

<table>
<tr><th>Study Type & Design</th><th>Objective (s) of the Study</th><th>Treatment</th><th>Results</th></tr>
<tr><td>clinical study</td><td>regarding efficacy, safety, and immunogenicity in subjects with Diabetic Macular Edema (DME)</td><td>every 8 weeks up to Week 48 (9 doses in total, with optional doses to continue at every 4 weeks)</td><td>to Week 8 based on 95% CI was fully contained within the interval (-3, 3) letters.
<table>
<tr><td></td><td colspan="2">Intention to treat (ITT)</td><td colspan="2">Per protocol (PP)</td></tr>
<tr><td></td><td>Yesafili
(N=179)</td><td>US-Eylea
(N=176)</td><td>Yesafili
(N=165)</td><td>US-Eylea
(N=161)</td></tr>
<tr><td>Adjusted mean (SE)</td><td>6.60
(0.548)</td><td>6.56
(0.548)</td><td>6.61
(0.556)</td><td>6.80
(0.565)</td></tr>
<tr><td>95% CI</td><td>(5.52, 7.68)</td><td>(5.48, 7.64)</td><td>(5.52, 7.70)</td><td>(5.69, 7.91)</td></tr>
<tr><td>Adjusted mean difference (SE)</td><td></td><td>0.04
(0.730)</td><td></td><td>-0.19
(0.745)</td></tr>
<tr><td>95% CI</td><td></td><td>(-1.40, 1.47)</td><td></td><td>(-1.66, 1.27)</td></tr>
</table>
Conclusion:
Biosimilarity was demonstrated based on the primary endpoint in both the ITT and PP Analysis Sets.</td></tr>
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2.3.2 Safety

- The overall incidence of treatment emergent adverse event (TEAE) was comparable between the study arms and the majority of TEAE was mild to moderate in severity.
- Most non-ocular TEAE were reported in both groups and in total in a low number of patients. The overall safety profile seems therefore acceptable and comparable in both treatment arms.
- The overall incidences of ocular TEAEs in the study eye were highly similar between treatment arms: 55/178 (30.9%) and 52/176 (29.5%) of subjects in the Yesafili and Eylea group, respectively.
- The majority of TEAEs were considered not related [in 231/354 (65.3%) of subjects] or unlikely [28/354 (7.9%) of subjects] related to study drug and there were no notable differences in frequencies between the treatment arms. All of the definitely related TEAEs were ocular TEAEs in study eye. Most of those are known undesirable effects of Eylea.
- The occurrence of ocular injection procedure related TEAEs was in line with known undesirable effects of Eylea and highly comparable between treatment arms.

- The overall safety profile of Yesafili is in line with known adverse events of Eylea. Some events were reported more frequently in the Yesafili arm, while others were more frequent in the Eylea arm, but no significant differences were observed. Therefore, biosimilarity is supported from a safety perspective.
- The overall immunogenicity profile appears to be lower for Yesafili compared to Eylea. Overall, no clinically relevant differences in the incidence of TEAEs was observed between ADA positive and ADA negative subjects or between study arms.

3.0 CONCLUSION

Drug Control Authority (DCA) on the 403th meeting on 2nd December 2024 has decided to approve the registration of this product with the following indication:

Yesafili is indicated for the treatment of

- neovascular (wet) age-related macular degeneration (wet AMD)
- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- visual impairment due to diabetic macular oedema (DME)
- visual impairment due to myopic choroidal neovascularisation (myopic CNV)