Ophthalmic VEGF inhibitor *Eylea® Solution for Intravitreal Injection 40 mg/mL* obtains approval for ROP as sixth indication

September 26, 2022, Osaka, Japan – Santen Pharmaceutical Co., Ltd. (hereinafter, “Santen”) and Bayer Yakuhin, Ltd. (head office: Osaka, Japan; hereafter "Bayer Yakuhin") announced today that, following an application by Bayer Yakuhin, they had obtained regulatory approval for an additional indication for ophthalmic Vascular endothelial growth factor (VEGF) inhibitor *"Eylea® Intravitreal Injection 40 mg/mL"* (aflibercept [recombinant] intravitreal injection; hereafter *"Eylea®"*) for retinopathy of prematurity (ROP).

Eylea® has already been approved in Japan for the indications of age-related macular degeneration with subfoveal choroidal neovascularization, macular edema associated with retinal vein occlusion, choroidal neovascularization in pathologic myopia, diabetic macular edema, and neovascular glaucoma. Retinopathy of prematurity is the sixth indication approved.

The application for approval was based on the results of the FIREFLEYE study, a global phase 3 study investigating the efficacy and safety of *Eylea®* administered intravitreally in an ROP patient group that included Japanese patients. The findings from the FIREFLEYE study were published in the Journal of the American Medical Association.

ROP is a vascular disease of the immature retina of babies born prematurely, and can lead to visual impairment and blindness in children. [1,2] The number of patients in Japan is reported to be about 5,000 per year.[3] Mild ROP usually resolves spontaneously, while severe forms of ROP require timely treatment.

"Due to the development of perinatal care, more premature babies are surviving, which is increasing the number of ROP cases and also the number of severe cases. ROP can lead to serious visual impairment and blindness and requires timely treatment,” said Dr. Noriyuki Azuma, president of the Japanese Association of Pediatric Ophthalmology. “I believe the addition of *Eylea®* as a new treatment option alongside existing therapies will be helpful for patients and healthcare professionals."

Eylea® will be distributed in Japan by Santen, with manufacturing and marketing authorization held by Bayer Yakuhin. Promotional activities for this drug will be conducted jointly by both companies.

Product Summary of *Eylea® Intravitreal Injection 40 mg/mL* (Underlined portion denotes newly added information)

Brand name	*Eylea® Solution for Intravitreal Injection 40 mg/mL*
Generic name	Aflibercept (recombinant)
Indications	Age-related macular degeneration with subfoveal choroidal neovascularization Macular edema associated with retinal vein occlusion Choroidal neovascularization in pathologic myopia Diabetic macular edema Neovascular glaucoma Retinopathy of prematurity
Dosage	**Age-related macular degeneration with subfoveal choroidal neovascularization** 2 mg (0.05 mL) of aflibercept (recombinant) administered intravitreally once every month for 3 consecutive months (loading dose period). In the maintenance period, the drug is usually administered by intravitreal injection once every 2 months. The dosing interval should be adjusted according to symptoms as needed but should be 1 month or longer. **Macular edema associated with retinal vein occlusion, choroidal neovascularization in pathologic myopia** 2 mg (0.05 mL) of aflibercept (recombinant) administered intravitreally. The dosing interval should be at least 1 month. **Diabetic macular edema** 2 mg (0.05 mL) of aflibercept (recombinant) administered intravitreally once every month for 5 consecutive months. Subsequently, the drug is usually administered by intravitreal injection once every 2 months. The dosing interval should be adjusted according to symptoms as needed but should be 1 month or longer. **Neovascular glaucoma** 2 mg (0.05 mL) of aflibercept (recombinant) administered intravitreally. The drug may be re-administered if necessary after a minimum interval of 1 month. **Retinopathy of prematurity** 0.4 mg (0.01 mL) of aflibercept (recombinant) administered intravitreally. The drug may be re-administered if necessary after a minimum interval of 1 month.
Date of marketing approval	September 28, 2012
Date of approval of additional	Macular edema associated with central retinal vein occlusion November 22, 2013

indications	Choroidal neovascularization in pathologic myopia September 19, 2014 Diabetic macular edema November 18, 2014 Macular edema associated with retinal vein occlusion June 26, 2015 Neovascular glaucoma March 25, 2020 Retinopathy of prematurity September 26, 2022
Manufactured and marketed by:	Bayer Yakuhin, Ltd.
Distributed by	Santen Pharmaceutical Co., Ltd.

Source

1) Results of Survey on persons with physical disability in 2006 (Ministry of Health, Labour and Welfare) https://www.mhlw.go.jp/toukei/saikin/hw/shintai/06/dl/01.pdf

2) Research study on causes of vision impairment of students in the special needs education school for the visually impaired in Japan and amblyopia classes of elementary schools and junior high schools - 2015 Survey – Report

http://www.human.tsukuba.ac.jp/~kakizawa/images/pdf/report.pdf

3) Japan Intractable Diseases Information Center, Retinopathy of Prematurity, 2009 (http://www.nanbyou.or.jp/entry/621, November 21, 2019)

About FIREFLEYE study

The FIREFLEYE study is a global phase 3 study investigating the efficacy and safety of *Eylea*® compared with retinal photocoagulation, the standard of care, in patients with retinopathy of prematurity (ROP). *Eylea*® showed a favorable benefit-risk profile in 113 patients, including Japanese patients, with ROP. The study assessed the non-inferiority of *Eylea*® 0.4 mg to retinal photocoagulation with respect to success criterion outside of Japan, with results showing that the response probability for the retinal photocoagulation group was 82.1%, while for the *Eylea*® 0.4 mg group it was 85.5%. The non-inferiority of the *Eylea*® 0.4 mg group to the retinal photocoagulation group was not verified (90% confidence interval for difference in response probability between groups: −8.0% to +16.2%). With respect to success criterion in Japan, the response rate (two-sided 95% confidence interval) of the Eylea® 0.4 mg group was 82.7% (72.2% - 90.4%) compared to a pre-specified threshold of 66%. For the *Eylea*® 0.4 mg group, the

lower limit of the confidence interval for the response rate exceeded 66%, verifying superiority to the pre-specified threshold. The safety profile was similar to that of the safety profile for the previously approved indications.

About Retinopathy of Prematurity (ROP)

Retinopathy of prematurity (ROP) is a vascular disease of the immature retina in babies born prematurely. Major risk factors for onset include short gestational age and low birth weight. Incomplete vessel growth triggers elevated intraocular levels of vascular endothelial growth factor (VEGF) and abnormal vessel growth. Mild ROP usually resolves spontaneously, while severe forms of ROP may lead to decreased vision or blindness and require timely treatment.

About VEGF aflibercept solution for injection into the eye

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring human protein that plays a role in promoting the formation of new blood vessels (angiogenesis) that support growth of body tissue and organs. It is also associated with the growth of abnormal new blood vessels in the eye, which exhibit abnormally elevated vessel permeability leading to edema.

Eylea® is a recombinant fusion glycoprotein, consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc domain of human IgG1, and formulated as an iso-osmotic solution for intravitreal administration. *Eylea*® acts as a soluble decoy receptor that by binding VEGF-A and Placental Growth Factor (PIGF) can inhibit the binding and activation of their cognate VEGF receptors.

Bayer and Regeneron Pharmaceuticals, Inc. are jointly conducting the global development of *Eylea*®. Regeneron maintains exclusive rights to *Eylea*® in the United States. Bayer has licensed the exclusive marketing rights outside the United States, with profits shared equally by the companies except in Japan, where Regeneron receives a percentage of net sales.

About Bayer

Bayer is a global enterprise with core competencies in the life science fields of health care and nutrition. Its products and services are designed to help people and planet thrive by supporting efforts to master the major challenges presented by a growing and aging global population. Bayer is committed to drive sustainable development and generate a positive impact with its businesses. At the same time, the Group aims to increase its earning power and create value through innovation and growth. The Bayer brand stands for trust, reliability and quality throughout the world. In fiscal 2021, the Group employed around 100,000 people and had sales of 44.1 billion euros. R&D expenses before special items amounted to 5.3 billion euros. For more information, go to www.bayer.com.

About Santen

As a specialized company dedicated to eye health, Santen carries out research, development, marketing, and sales of pharmaceuticals, over-the-counter products, and medical devices, and its products now reach patients in over 60 countries and regions.

Toward realizing “WORLD VISION” (Happiness with Vision), the world Santen ultimately aspires to achieve, as a “Social Innovator”, we aim to reduce the social and economic opportunity loss of people around the world caused by eye diseases and defects by orchestrating and mobilizing key technologies and players around the world.

With scientific knowledge and organizational capabilities nurtured over a 130-year history, Santen provides products and services to contribute to the well-being of patients, their loved ones and consequently to society.

For more information, please visit Santen’s website (https://www.santen.com/en/).

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