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U.S. FDA approves updated Novartis BEOVU® label, to include additional safety information

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- *Novartis worked with U.S. Food and Drug Administration (FDA) to update BEOVU (brolucizumab-dbll) prescribing information to guide healthcare professionals in their treatment of wet AMD patients*[1]
- *The update includes characterization of adverse events, retinal vasculitis and retinal vascular occlusion, as part of the spectrum of intraocular inflammation observed in the HAWK & HARRIER trials and noted in the original prescribing information*[1]
- *Novartis has convened a fully dedicated team collaborating with top global external experts, leveraging the collective multidisciplinary expertise to examine the root causes, potential risk factors and mitigation of these adverse events*[2]
- *A Safety Review Committee established by Novartis noted that the overall rate of vision loss in the study population was similar between the BEOVU and aflibercept arms in HAWK & HARRIER despite the risk of vision loss associated with the adverse events of interest*[2]
- *Novartis is confident that BEOVU continues to represent an important treatment option for patients with wet AMD, with an overall favorable benefit/risk profile*

East Hanover, June 11, 2020 - Novartis announced today that the U.S. Food and Drug Administration (FDA) has approved a label update for BEOVU® (brolucizumab-dbll) to include additional safety information regarding retinal vasculitis and retinal vascular occlusion[1]. This approval follows Novartis' announcement that it would pursue worldwide label updates after a review and further characterization of rare post-marketing safety events reported to Novartis. This is one of many efforts Novartis is taking to help physicians to make informed decisions on the use of BEOVU, including the establishment of a fully dedicated internal team collaborating with top global experts (a coalition) to examine the root causes, risk factors, mitigation and potential treatment protocols[2].

The update to the U.S. label includes the addition of a sub-section dedicated to retinal vasculitis and/or retinal vascular occlusion under 'Warnings and Precautions' (section 5)[1]. It also specifies that these adverse reactions are part of a spectrum of intraocular inflammation rates from the Phase III HAWK & HARRIER trials (Table 1)[1].

"This label update provides clinicians with important information to guide treatment decisions. We believe BEOVU continues to represent an important treatment option for patients with wet AMD, with an overall favorable benefit-risk profile," said Marcia Kayath, Global Head of Medical Affairs and Chief Medical Officer, Novartis Pharmaceuticals. "We remain grateful to all doctors who have taken the time to share their expertise and treatment experience to contribute to the collective understanding of these safety events. As we proceed to examine root causes and potential mitigation strategies, we will continue to communicate findings with transparency and urgency to regulatory bodies and healthcare providers."

BEOVU was approved in the U.S. in October 2019 for the treatment of wet age-related macular degeneration (AMD), based on findings from the Phase III HAWK and HARRIER clinical trials, in which BEOVU demonstrated non-inferiority versus aflibercept in mean change in best-corrected visual acuity (BCVA) at year one (week 48)[1,3]. BEOVU is the first anti-VEGF to offer both greater fluid resolution versus aflibercept and the ability to maintain eligible wet AMD patients on a three-month dosing interval immediately after a three-month loading phase with uncompromised efficacy[1,3].

In early 2020, following receipt by Novartis of rare post-marketing reports of vasculitis, including retinal occlusive vasculitis, Novartis initiated its own internal review of these post-marketing safety case reports including the establishment of an external Safety Review Committee (SRC) to provide an independent, objective review of these cases and a comparison with select intraocular inflammation events seen in the brolucizumab Phase III trials (HAWK & HARRIER)[2].

The SRC recently issued a report of its unmasked, independent analysis of HAWK & HARRIER adverse events, finding that cases similar to those reported post-marketing were present in the HAWK & HARRIER clinical studies[2]. The report also noted that the overall rate of vision loss in the study population was similar between the brolucizumab and aflibercept arms in HAWK & HARRIER despite the risk of vision loss associated with the adverse events of interest[2].

Novartis continues to work with global regulatory authorities to initiate safety information updates to BEOVU prescribing information worldwide. BEOVU has now been approved in more than 30 countries. BEOVU also recently received positive Health Technology Assessment Reviews (HTA) in countries such as Canada4 and is now fully reimbursed in multiple countries including Japan and Switzerland[5,6]. Novartis remains confident in BEOVU as an important treatment option for patients with wet AMD.

Coalition convened as part of ongoing commitment to patient safety

A fully dedicated team of Novartis research, drug development and medical specialists are working with a team of top global experts to examine the root causes and potential risk factors associated with the reported adverse events and to determine mitigation and treatment recommendations[2].

"This broad-based coalition, which includes clinical trialists, epidemiologists, immunologists and uveitis specialists, is exploring innovative approaches to analyzing every aspect of available data, with the goal of providing physicians tools and information to safely and confidently treat their patients with BEOVU," said Dr. Jeff Heier, Co-President and Medical Director, Director of the Vitreoretinal Service, and Director of Retina Research at Ophthalmic Consultants of Boston, Chair of the Safety Review Committee and a member of the coalition.

Novartis encourages physicians to continue to report any adverse or suspicious events in accordance with local requirements at https://www.report.novartis.com. Novartis remains committed to transparency and will continue to provide updates on https://www.brolucizumab.info as information becomes available.

About BEOVU (brolucizumab-dbll)

BEOVU (brolucizumab-dbll, also known as RTH258) is the most clinically advanced humanized single-chain antibody fragment (scFv)[3,7]. Single-chain antibody fragments are highly sought after in drug development due to their small size, enhanced tissue penetration, rapid clearance from systemic circulation and drug delivery characteristics[7-9].

The proprietary innovative structure results in a small molecule (26 kDa) with potent inhibition of, and high affinity to, all VEGF-A isoforms[8]. BEOVU is engineered to deliver a high concentration of drug, thus providing more active binding agents[3,7]. In preclinical studies, BEOVU inhibited activation of VEGF receptors through prevention of the ligand-receptor interaction[8-10]. Increased signaling through the VEGF pathway is associated with pathologic ocular angiogenesis and retinal edema[11]. Inhibition of the VEGF pathway has been shown to inhibit the growth of neovascular lesions and suppress endothelial cell proliferation and vascular permeability[11].

About the HAWK and HARRIER studies

With more than 1,800 patients across nearly 400 centers worldwide, HAWK (NCT02307682) and HARRIER (NCT02434328) are the first global head-to-head trials in patients with wet AMD that prospectively demonstrated efficacy at week 48 using an innovative q12w/q8w regimen, with a majority of patients on q12w immediately following the loading phase. Both studies are 96-week prospective, randomized, double-masked multi-center studies and part of the Phase III clinical development of BEOVU[3]. The studies were designed to compare the efficacy and safety of intravitreal injections of brolucizumab 6 mg (HAWK and HARRIER) and 3 mg (HAWK only) versus aflibercept 2 mg in patients with wet AMD. The most common adverse events (>=5% of patients) with BEOVU were vision blurred, cataract, conjunctival hemorrhage, vitreous floaters and eye pain[3].

About wet age-related macular degeneration

Wet AMD is the leading cause of severe vision loss and legal blindness in people over the age of 65 in North America, Europe, Australia and Asia, impacting an estimated 20 million people worldwide[12-14]. Wet AMD occurs when abnormal blood vessels form underneath the macula, the area of the retina responsible for sharp, central vision[15-17]. These blood vessels are fragile and leak fluid, disrupting the normal retinal architecture and ultimately causing damage to the macula[15-17].

Early symptoms of wet AMD include distorted vision (or metamorphopsia) and difficulties seeing objects clearly[18]. Prompt diagnosis and intervention are essential[17]. As the disease progresses, cell damage increases, further reducing vision quality[15]. This progression can lead to a complete loss of central vision, leaving the patient unable to read, drive or recognize familiar faces and potentially depriving them of their independence[15,19]. Without treatment, vision can rapidly deteriorate20.

About Novartis in ophthalmology

At Novartis, our mission is to discover new ways to improve and extend people's lives. In ophthalmology, we develop and deliver life-changing medicines and therapies for diseases and conditions from front to back of the eye, enabled by data and transformative technologies. Our ophthalmic solutions reach more than 150M people per year, from premature infants to the elderly.

About Novartis

Located in East Hanover, NJ Novartis Pharmaceuticals Corporation – an affiliate of Novartis – is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis employs about 15,000 people in the United States. For more information, please visit http://www.novartis.us.

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Source URL: *https://www.novartis.com/us-en/news/media-releases/us-fda-approves-updated-novartis-beovu-label-include-additional-safety-information*

List of links present in page

- https://www.novartis.com/us-en/us-en/news/media-releases/us-fda-approves-updated-novartis-beovu-label-include-additional-safety-information
- https://www.novartis.com/news/novartis-completes-safety-review-and-initiates-update-beovu-prescribing-information-worldwide
- https://www.report.novartis.com/
- https://www.brolucizumab.info/
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