Report ORLADEYO® Berotralstat

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: Berotralstat **Brand Name:** Orladeyo™ **Originator/licensee:** BioCryst Ireland Limited **Classification:** NCE **ATC code:** B06AC06 **Orphan Status:** **Eu:** Yes **Us:** Yes **Mechanism of action:** Berotralstat is a plasma kallikrein inhibitor that binds to plasma kallikrein and inhibits its proteolytic activity. Plasma kallikrein is a protease that cleaves HMWK to generate cHMWK and bradykinin, a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with HAE.Berotralstat decreases plasma kallikrein activity to control excess bradykinin generation in pts with HAE[1].	**Authorized Indication:** **EMA:** berotralstat is indicated for routine prevention of recurrent attacks of HAE in adult and adolescent pts aged 12 years and older [2]. **FDA:** berotralstatis indicated for prophylaxis to prevent attacks of HAE in adults and pediatric pts 12 years of age and older [1]. **Route of administration:** OS **Licensing status** **EU CHMP P.O. date:** 25/02/2021 **FDA M.A. date:** 12/03/2020 **EU Speed Approval Pathway:**No **FDA Speed Approval Pathway:** No --- **ABBREVIATIONS:** **AE:** Adverse Event **AE-QoL:** Angioedema Quality of Life Questionnaire **CHMP:** Commettee for Medicinal Product for Human Use **cHMWK:** cleaved HMWK **EAACI**: European Academy of Allergy and Clinical Immunology **HAE:** Hereditary Angioedema **HMWK:** High-Molecular-Weight-Kininogen **LSM**: Least Squares Mean **M.A.**: Marketing Authorization **mEDRA**: Medical Dictionary for Regulatory Activities **P.O**: Positive Opinion **pts:** patients **SOC:** Standard of Care **TEAE:**Treatment-Emergent Adverse Event **TESAE:** Treatment-Emergent Severe Adverse Event **vs**.: versus **WAO**: World Allergy Organization	**Summary of clinical EFFICACY:** **Trial 1 (NCT03485911)**: The efficacy of berotralstat for the prevention of angioedema attacks in pts 12 years of age and older with Type I or II HAE was demonstrated in part one of a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The study included 120 adult and adolescent pts who experienced at least two investigatorconfirmed attacks within the first eight weeks of the run-in period and took at least one dose of study treatment. Pts were randomized into one of three parallel treatment arms, stratified by baseline attack rate, in a 1:1:1 ratio (berotralstat 110 mg, berotralstat 150 mg, or placebo by oral administration once daily, with food) for the 24-week treatment period. The primary endpoint was the rate of investigator-confirmed HAE attacks during the treatment period. Berotralstat demonstrated a significant reduction in attacks at both dose levels compared to placebo: 1.65 attacks per month at 110 mg (p =.024); 1.31 attacks per month at 150 mg (p<.001) and 2.35 attacks per month with placebo. Secondary end points were the change from baseline in AE-QoL total scores at week 24: this was not significant vs. placebo (LSM difference from placebo: –2.77 [95% CI = –10.08 to 4.53] points in the 110- mg dose of berotralstat group [P = .453] and –4.90 [95% CI = –12.23 to 2.43] points in the 150-mg dose of berotralstat group [P = .188]) [3]. **Summary of clinical SAFETY:** The percentage of pts experiencing at least one TEAE was similar in all three arms over the 24-week period (83% with the 110-mg dose of berotralstat, [n = 34]; 85% with the 150-mg dose of berotralstat, [n = 34]; and 77% with placebo, [n = 30]). The TEAEs that occurred most commonly (>10% in any treatment group) and more frequently with berotralstat (>2 pts difference in either arm compared in the placebo arm) on study were abdominal pain, vomiting, diarrhea, and back pain. Gastrointestinal abdominal TEAEs (any AE with a preferred term within the mEDRA, version 19.1, hierarchy under the high-level group terms of “GI signs and symptoms” or “GI motility and defecation conditions”) were generally grade 1 or 2 and self-limited. Events of vomiting, diarrhea, or abdominal pain had a median duration of two days in the 150-mg of berotralstat arm (95% CI = 1.0-7.0) vs oneday in the placebo arm (95% CI = 0.0-7.0). Gastrointestinal abdominal TEAEs occurredprimarily within the first month of treatment. All TESAEs were reportedby the investigators as unrelated to the study drug[3]. **Ongoing studies:** ● ***For the same indication:*** Yes [4] ● ***For other indications:*** No [4] [Phase III, but if it is an O/OE drug, also Phase II] **Discontinued studies (for the same indication):** No [4]	**Cost of therapy:** Biocryst set the wholesale acquisition cost at $485,004 annually, or $37,308 per 28-day pack of either 150-mg or 110-mg capsules[5]. **Epidemiology:** In 2013 the minimum estimated prevalence of HAE in Italy was 920/59.394.000 inhabitants, equal to 1/64.935[6]. --- **POSSIBLE PLACE IN THERAPY** The international WAO/EAACI guideline for the management of HAE recommends the use of C1-Inhibitors for first line long term prophylaxis and suggests to use androgens as second-line long-term prophylaxis. [7] **OTHER INDICATIONS IN DEVELOPMENT:** No **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** No **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Yes (Garadacimab, C1INH-nf) *Service reorganization Y/N: No *Possible off label use Y/N: No --- **References:** **1**.https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214094s000lbl.pdf **2.**https://www.ema.europa.eu/en/medicines/human/summaries-opinion/orladeyo-0 **3**. Zuraw B, etal. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial. J Allergy Clin Immunol. 2020 Oct 21:S0091-6749(20)31484-6. doi: 10.1016/j.jaci.2020.10.015. **4.**https://clinicaltrials.gov/ **5.**https://www.bioworld.com/articles/500936-biocrysts-orladeyo-cleared-for-hae-priced-high-is-oral-appeal-enough **6.**https://www.osservatoriomalattierare.it/malattie-rare/angioedema-ereditario/7779-angioedema-ereditario-studio-italiano-esegue-sondaggio-su-pazienti-con-carenza-dellinibitore-c1#:~:text=La%20prevalenza%20minima%20stimata%20in,da%20Angioedema%20Ereditario%20C1%2DINH. **7.**https://waojournal.biomedcentral.com/articles/10.1186/s40413-017-0180-1#Sec13

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