Report OZAWADE® pitolisant

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: pitolisant **Brand Name:** OZAWADE® **Originator/licensee:** BIOPROJET PHARMA **Classification:** NCE **ATC code:** N07XX11 **Orphan Status:** **Eu:** No **Us:** - **Mechanism of action:** pitolisant is a H3-receptor antagonist/inverse agonist which enhances the activity of brain histaminergic neurons [1].	**Authorized Indication:** **EMA:** pitolisant is indicated to improve wakefulness and reduce EDS in adult pts with OSA whose EDS has not been satisfactorily treated by, or who have not tolerated, OSA primary therapy, such as CPAP [1]. **Route of administration:** OS **Licensing status** **EU CHMP P.O. date:** 20/5/2021 **FDA M.A. date:** - **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** - ----- **ABBREVIATIONS:** **CHMP:** Committee for Medicinal Products for Human Use **CPAP:** continuous positive airway pressure **ECG:** Electrocardiogram **EDS:** excessive daytime sleepiness **ESS** (Epworth Sleepiness Scale)**:** is the sum of 8 item scores (0-3) and can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life, or their 'daytime sleepiness'. **H3**: histamine H3-receptor **ITT:** intention-to-treat **M.A.:** Marketing Authorization **OSA:** obstructive sleep apnoea **P.O.:** Positive Opinion **pts:** patients **TEAEs:** Treatment-Emergent Adverse Events **vs**.: versus	**Summary of clinical EFFICACY:** **Harosa I (NCT01071876)** is a multicenter, double-blind, randomized, placebo-controlled, phase 3 trial. Adult pts (n=244) with moderate-to-severe OSA, treated with CPAP for at least three months with persistence of EDS despite mean nightly CPAP use of at least four hours, were randomized 3:1 to receive pitolisant (n=183) or placebo (n=61). Pitolisant treatment was initiated at 5 mg and titrated individually at up to 20 mg/day and taken over 12 weeks. The primary endpoint was change from baseline to week 12 in the ESS score in the ITT population. The change in ESS from baseline to end of treatment was -5.5 (95% CI, -6.2 to -4.9) in the pitolisant group and -2.8 (95% CI, -4.3 to -1.2) in the placebo group (p<0.001). The difference in ESS score between pitolisant and placebo groups was -2.6 (95% CI, -3.9 to -1.4; p<0.001) [2]. **Harosa II (NCT01072968)** is a multicenter, double-blind, randomized, placebo-controlled, phase 3 trial. Adult pts (n=268) with moderate-to-severe OSA, experiencing EDS, refusing or not adhering to CPAP therapy, were randomized 3:1 to receive pitolisant (n=201) or placebo (n=67). Pitolisant treatment was initiated at 5 mg and titrated individually at up to 20 mg/day and taken over 12 weeks. The primary endpoint was change from baseline to week 12 in the ESS score in the ITT population. The change in ESS from baseline to end of intervention was -6.3 (95% CI, -6.92 to -5.66) in the pitolisant group and -3.6 (95% CI, -4.92 to -2.25) in the placebo group (p<0.001). The difference in ESS score between pitolisant and placebo groups was -2.8 (95% CI, -4.0 to -1.5; p<0.001) [3]. **Summary of clinical SAFETY:** **Harosa I (NCT01071876):** the incidence of any TEAEs was 47.0% in the pitolisant group and 32.8% in the placebo group (p=0.03). The most frequently reported TEAE was headache (14.8% and 11.5% for pitolisant and placebo group, respectively). Insomnia was reported in 9.3% of pts in the pitolisant arm vs. 3.3% in the placebo arm. The frequency for treatment-related TEAEs was 26.8% in the pitolisant arm vs. 19.7% in the placebo arm. Serious TEAEs (irritable bowel syndrome and musculoskeletal pain) were reported in two pts in the pitolisant arm (1.1%), none in the placebo arm. TEAEs leading to study drug withdrawal were reported for four participants (2.2%) in the pitolisant arm vs. two (3.3%) in the placebo arm [2]. **Harosa II(NCT01072968):** the incidence of any TEAEs was 29.5% in the pitolisant group and 25.4% in the placebo group, respectively. The most frequently reported TEAE was headache (8.5% and 11.9% in the pitolisant and placebo groups, respectively). Other frequent TEAEs were insomnia (5.5% in the pitolisant arm vs. 3.0% in the placebo), nausea (2.5% vs. 1.5%), vertigo (2.0% for both arms). The frequency for treatment-related TEAEs was 24.0% in the pitolisant group vs. 19.4% in the placebo group. Serious TEAEs were reported for two pts (1.0%) in the pitolisant arm (one prolonged QT interval on the ECG and one cardiopulmonary failure leading to death) and none of the pts receiving placebo. TEAEs leading to study drug withdrawal were reported in 1.5% of pts in the pitolisant arm vs. 3.0% pts in the placebo arm [3]. **Ongoing studies:** ● ***For the same indication:*** No. HarosaIII (NCT02739568) completedbut no results yet. ● ***For other indications:*** Yes **Discontinued studies (for the same indication):** Yes (NCT02978651) ----- **References:** [1]. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/ozawade [2]. Pépin J.L., Georgiev O., et al.: Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP: A Randomized Trial. Chest. 2021;159(4):1598-1609. [3]. Dauvilliers Y., Verbraecken J., et al.: Pitolisant for Daytime Sleepiness in Patients with Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment: a randomized trial. AM J Respir Crit Care Med. 2020;201(9):1135-1145. [4]. Benjafield A.V., Ayas N.T., et al.: Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med 2019; 7: 687–98. [5]. https://www.nice.org.uk/guidance/gid-ta10430/documents/129 [6].https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_004165_048446_RCP.pdf&retry=0&sys=m0b1l3 [7]. https://adisinsight.springer.com/search [8].https://clinicaltrials.gov/ct2/results?cond=Obstructive+Sleep+Apnea&term=&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=	**Cost of Therapy:** Not available. **Epidemiology:** Nearly 1 billion adults aged 30–69 years worldwide were estimated to have OSA, with 425 million (>45%) of these individuals having moderate-to-severe OSA. In Italy, about 20.5% of people aged 30-69 years have OSA and 12% have moderate-to-severe OSA [4]. ----- **POSSIBLE PLACE IN THERAPY** CPAP is the first-line therapy for symptomatic moderate-to-severe OSA; however, residual EDS is known to persist in approximately 15% of pts. Wake-promoting agents such as solriamfetol have been approved in the USA and in Europe as adjunct to CPAP for the treatment of residual sleepiness in individuals with OSA [2] [5] [6]. **OTHER INDICATIONS IN DEVELOPMENT** EDS in pts with myotonic dystrophy type 1 (NCT04886518), Prader-Willi syndrome (NCT04257929),pediatric narcolepsy (NCT02611687). **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** / **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION** BAY2586116, oxybutynin/atomoxetine, AD113, AD504, AD182, acetazolamide/eszopiclone [7,8]. *Service reorganization: No *Possible off label use: Yes

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