Report VAZKEPA® Icosapent ethyl

Product Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: Icosapent ethyl (AMR101) **Brand Name:** C10AX06 (Vascepa® in USA) **Originator/licensee:** Amarin Pharmaceuticals Ireland Limited **Classification:** NCE **ATC code:** C10AX06 **Orphan Status:** **EU:** No **USA:** No **Mechanism of action:** Icosapent ethyl acts as a pro-drug for EPA, as it is hydrolyzed enzimatically by esterases to liberate the free acid EPA. The latter's mechanisms of action are multi-factorial, and include an improved lipoprotein profile caused by the reduction of triglyceride-rich lipoproteins (TRL-C), anti-inflammatory and antioxidant effects, reduction of macrophage accumulation, improved endothelial functions, increased fibrous cap thickness and antiplatelet effects. [1]	**Authorized Indication** **FDA:** Icosapent is indicated as an adjunct to diet to reduce TG levels in adult pts with severe (≥500 mg/dL) hypertriglyceridemia. [1] **EMA:** Icosapent is indicated to reduce the risk of cardiovascular events in adult statin-treated pts at high cardiovascular risk with elevated TG (≥150 mg/dL) and established cardiovascular disease, or diabetes, and at least one other cardiovascular risk factor. [2] **Route of administration:** OS **Licensing status** **EU CHMP positive opinion date:** 28/01/2021 **FDA M.A. date:** 13/12/2019 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** No ----- **ABBREVIATIONS:** **ALT**: alanine aminotransferase **ApoB**: apolipoprotein B **ASCVD**: atherosclerotic cardiovascular diseases **CNS**: central nervous system **EPA**: eicosapentaenoic acid **HTG**: hypertriglyceridemia **ITT:** Intention-To-Treat **Lp-PLA2**:lipoprotein-associated phospholipase A2 **Non-HDL-C**: non-HDL cholesterol **Pts: patients** **QALY**: quality adjusted life years **SAE**: serious adverse events **TG**: triglycerides **TRL-C**: triglyceride-rich lipoproteins **VLDL-TG**: very low density lipoprotein – TG **VLDL-C**: very low density lipoproteins- cholesterol	**Summary of clinical EFFICACY:** **Phase III, MARINE trial (NCT01047683)** This was a multi-center, placebo-controlled, randomized, double-blind, 12-week study conducted on 229 pts who had fasting TG levels ≥ 500 mg/dl and ≤ 2000 mg/dl. The subjects started a 4- to 6- week diet stabilization period and they subsequently entered a 2-week TG qualifying period where they were randomized to either placebo, 2g Icosapent or 4g Icosapent for 4 weeks. After this period, pts entered a 40-week, open label extension period and received 4g/day Icosapent. The primary end point was the placebo-corrected median percentage of change in TG from baseline to study end (week 12) in the two active treatment groups vs placebo. The median percent changes in fasting TG levels were 9.7% in placebo, -7.0% in Icosapent 2 g/day and -26.6% in Icosapent 4 g/day. In the ITT-population, Icosapent 4 g/day reduced placebo-corrected median TG levels by 33.1% (p <0.0001); Icosapent 2 g/day reduced placebo-corrected median TG levels by 19.7% (p = 0.0051) [1] [4] **Phase III, ANCHOR trial (NCT01047501)** aimed to assess the efficacy and safety of two doses of icosapent ethyl on fasting TG levels in pts on statins with high TG levels (≥200 and <500 mg/dl). This was a multi-center, placebo-controlled, randomized, double-blinded, 12-week clinical trial. Pts were required to have been on ≥4 weeks of stable statin therapy and continue such treatment during the study. The subjects underwent a lead-in period of 4- to 6- weeks to stabilize their diet and lifestyle. Subsequently, they entered a 2- to 3- weeks qualifying period. Approximately 216 pts were then randomized one week later to Icosapent 4g/day, Icosapent 2g/day or placebo. The primary end point was median percent change in TG levels from baseline vs placebo after 12 weeks. In the primary efficacy analysis, the median placebo-adjusted change from the baseline was -21.5% in Icosapent 4 g/day (p<0.0001) and -10.1% in Icosapent 2 g/day (p=0.0005). [1] [3] **Summary of clinical SAFETY:** The most common side effects were bleeding (there were five reports of anemia with Icosapent vs none with placebo), arthralgia (2.6% with Icosapent vs 1.3% with placebo) and oropharyngeal pain(1.3% with Icosapent vs 0.3% with placebo). Among pts treated with Icosapent, 12.8% reported mild elevations of ALT vs 10.3% of the subjects treated with placebo. There was one reported death of a patient participating in the ANCHOR trial and randomized to placebo. The incidence of nonfatal SAEs was 2.9% in the Icosapentpooled group and 1.6% in the placebo group. Moreover, there was no clear association with the dose ofIcosapent and the development of any SAE. [1] **Ongoing studies:** ● ***For the same indication:*** Yes ● ***For other indications:*** Yes *[Phase III, but if it is an O/OE drug, also Phase II]* **Discontinued studies (for the same indication):** No **References:** [1]. https://www.fda.gov/ [2]. https://www.ema.europa.eu/en [3]. Ballantyne CM et al., Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am J Cardiol. 2012 Oct 1;110(7):984-92. doi: 10.1016/j.amjcard.2012.05.031. [4]. Bays H.E. MD, Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Patients With Very High Triglyceride Levels (from the Multi-center, placebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] Trial). The American Journal of Cardiology, 2011-09-01, Fascicolo 108, Numero 5, Pagine 682-690, Copyright © 2011 Elsevier Inc. [5]. http://careonline.it/wp-content/uploads/2011/07/SIReCS.pdf [6]. https://www.simg.it/Riviste/rivista_simg/2017/04_2017/5.pdf [7]. https://emedicine.medscape.com/article/126568-treatment#d8 [8]. https://www.globenewswire.com/news-release/2019/11/11/1944891/0/en/New-Analysis-Shows-Icosapent-Ethyl-Vascepa-Is-Cost-Effective-and-Offers-Rare-Finding-of-Better-Outcomes-at-Lower-Healthcare-Costs-When-Used-to-Treat-High-Risk-Patients-with-Cardiov.html [9]. https://www.drugs.com/price-guide/vascepa [10].https://clinicaltrials.gov/ct2/results?cond=&term=&type=Intr&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=Vascepa&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [11].https://clinicaltrials.gov/ct2/results?cond=Hypertriglyceridemia&term=&type=Intr&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [12] https://www.springerhealthcare.it/wp-content/uploads/2018/12/Infocus-IBSITCR500081.pdf	**Cost of therapy:** $368.86 for 120 capsules (1 g) –US[9]. The recommended dose of Icosapent is 4 g/day, as two 1 g capsules twice a day.[1] *Price for 1 month 4 g/day Icosapent therapy: 368,33 $* Icosapent offers better outcomes at lower healthcare costs (below 50.000$ per QALY gained). [8] **Epidemiology:** Hypertriglyceridemia (defined as presence of plasmatic TG levels ≥ 200 mg/dl) is a frequent clinical condition. It is estimated that in Italy 1/3 adult has high blood TG (data extracted from ISS database). [12] Familiar HTG has a prevalence of 1:500, and its diagnosis includes 250-2000 mg/dl TG levels, slightly increased cholesterol levels and reduced HDL levels. [5] [6] ----- **POSSIBLE PLACE IN THERAPY** In addition to lifestyle intervention, the use of high doses of a strong statin (simvastatin, atorvastatin, rosuvastatin) lower triglycerides, by as much as approximately 50%, and raise high-density lipoprotein (HDL) cholesterol.In addition to statins, three classes of medications are appropriate for the management of major triglyceride elevations: fibric acid derivatives, niacin, and omega-3 fatty acids. [7] **OTHER INDICATIONS IN DEVELOPMENT:** colorectal cancer liver metastases (CRCLM), COVID-19, Alzheimer's disease. [10] **SAME INDICATION IN EARLIER LINE(S) OF TRETMENT:** No **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** MAT9001 (omega-3 pentaenoic acid), MND-2119 (icosapent). [11] *Service reorganization Y/N No *Possible off label use Y/N Yes

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