Report REPATHA® evolocumab

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: evolocumab **Brand Name:** Repatha **Originator/licensee:** Amgen Europe B.V. **Classification:** NI **ATC code:** C10AX13 **Orphan Status**: Eu: No Us: Yes **Mechanism of action**: Evolocumab is a monoclonal antibody that selectively binds to PCSK9, a protein that attaches to LDLRs on the surface of hepatocytes and causes the degradation of these receptors. By blocking PCSK9, evolocumab prevents the PCSK9-mediated degradation of LDLR. The increase in hepatic levels of LDLR determines the reduction of serum LDL-C levels [1].	**Authorized Indication:** **EMA:** Evolocumab is indicated in paediatric pts aged 10 years and over with HeFH, as an adjunct to diet: -in combination with a statin or statin with other lipid-lowering therapies in pts unable to reach LDL-C goals with the maximum tolerated dose of a statin, or -alone or in combination with other lipid-lowering therapies in pts who are statin-intolerant, or for whom a statin is contraindicated. [2] **FDA**: Evolocumab is indicated as an adjunct to diet and other LDL-C-lowering therapies in pediatric pts aged 10 years and older with HeFH, to reduce LDL-C. [3] **Route of administration:** SC **Licensing status** **EU CHMP P.O. date:** 14/10/2021 **FDA M.A. date:** 24/09/2021 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** No **ABBREVIATIONS:** **AEs:** Adverse events **CHMP:** Commettee for Medicinal Products for Human Use **HeFH:** Heterozigous Familial Hypercholesterolemia **LDL-C:** Low Density Lipoprotein-Cholesterol **LDLR:** Low Density Lipoprotein Receptor **MA:** Marketing Authorization **PCSK9**: Proprotein Convertase Subtilisin/Kexin type 9 **PO**: Positive Opinion **pts**: patients **sc**: subcutaneous	**Summary of clinical EFFICACY:** **NCT02392559** is a phase 3, randomized, double-blind, placebo-controlled, 24-week trial to evaluate the efficacy and safety of evolocumab in pediatric pts (aged 10-17 years) with HeFH. At baseline, 99% (156/157) of pts were using statins, and 13% were also taking ezetimibe. No changes in background lipid-lowering therapy were reported at any time during the trial. Pts were randomized to receive either monthly SC injections of evolocumab 420mg (n=104) or placebo (n=53). The primary endpoint was the percentage change in LDL-C level from baseline to week 24. At week 24, the mean percent change in LDL-C level was −44.5% in the evolocumab group and −6.2% in the placebo group, for a difference of −38.3% (p<0.001) [4]. **Summary of clinical SAFETY:** During the **NCT02392559** trial, AEs occurred in 62% of the pts treated with evolocumab vs 64% of those in the placebo group, while 1% vs 0 experienced serious AEs. 1% of the pts in the evolocumab arm vs 0 subjects in the placebo group discontinued the study regimens due to AEs. The most common AEs across the evolocumab group vs the placebo group were nasopharyngitis (12% vs 11%), headache (11% vs 2%), oropharyngeal pain (7% vs 0), influenza (6% vs 4%) and upper respiratory tract infection (6% vs 2%). [4] **Ongoing studies:** ● ***For the same indication: Yes**** ● ***For other indications: Yes*** **Discontinued studies (for the same indication):** ***Yes***** ***Notes***: **Open-label extension of pivotal trial NCT02392559. Completed in June 202, results not yet available. 1* [5] ***Discontinued trial: *NCT03331666, trial to assess the impact of evolocumab on platelet function of FH patients. Actual enrollment: 4 participants. Terminated prematurely due to COVID-19* [5]. **References:** 1.https://www.ema.europa.eu/en/documents/overview/repatha-epar-summary-public_en.pdf 2.https://www.ema.europa.eu/en/medicines/human/summaries-opinion/repatha-0 3.https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/125522Orig1s031ltr.pdf 4. https://pubmed.ncbi.nlm.nih.gov/32865373/ 5. https://clinicaltrials.gov/ 6. https://gallery.farmadati.it/ 7.https://www.ema.europa.eu/en/documents/product-information/repatha-epar-product-information_en.pdf 8.https://www.giornaledicardiologia.it/archivio/2254/articoli/24280/ 9. https://pubmed.ncbi.nlm.nih.gov/31536851/ 10. https://pubmed.ncbi.nlm.nih.gov/29877295/ 11. https://www.ema.europa.eu/en/medicines	**Cost of therapy:** In Italy, the price ex-factory of a 140mg pre-filled pen is 196,15€ [6]. The dosage of 420mg should be administered using three 140mg pens consecutively [7], that corresponds to a monthly cost of 588,45€. **Epidemiology:** Based on updated prevalence of approximately one in 200 people, in Italy there are about 250,000-300,000 subjects with HeFH. [8] **POSSIBLE PLACE IN THERAPY** Statins are the first-line drugs for children and young people with HeFH. In pts who do not achieve the LDL-C targets with the statin alone, adding ezetimibe is recommended. Bile acid sequestrants such as colestyramine are normally not used in children [9-10]. Evolocumab should therefore represent a third-line therapy for pediatric pts with HeFH unable to reach LDL-C goals with a statin or statin with other lipid-lowering therapies, and it would represent a treatment option alone or in combination with other lipid-lowering therapies in pts who are statin-intolerant, or for whom a statin is contraindicated. **OTHER INDICATIONS IN DEVELOPMENT:** Prevention of cardiac allograft vasculopathy, COVID-19 [5]. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: No** **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION (HeFH):** •Recent EU M.A. for adult pts with HeFH, not yet available on Italian market: Bempedoic acid, Bempedoic acid / Ezetimibe combination, Inclisiran [11]. •Ongoing phase III trials: Lerodalcibep (Eligibility Criteria: ≥10 years), Tafolecimab (Eligibility Criteria: 18-80 years) [5].

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