Report LORVIQUA® lorlatinib

Product &Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: lorlatinib **Brand Name:** Lorviqua **Originator/licensee:** Pfizer Europe MA EEIG **Classification:** NI **ATC code:** L01ED05 **Orphan Status:** **Eu:** No **Us:** Yes **Mechanism of action:** Lorlatinib is a selective, ATP-competitive inhibitor of ALK and ROS1 tyrosine kinases. Lorlatinib demonstrated *in vitro* activity against multiple mutant forms of the ALK enzyme, including some mutations detected in tumors at the time of disease progression on crizotinib and other ALK inhibitors. Moreover, lorlatinib possesses the capability to cross the blood-brain barrier, allowing it to reach and treat progressive or worsening brain metastases as well. The overall antitumor activity of lorlatinib in *in-vivo* models appears to be dose-dependent and correlated with the inhibition of ALK phosphorylation [1, 2].	**Authorized Indication:** **EMA:** lorlatinib as monotherapy is indicated for the treatment of adult pts with ALK positive advanced NSCLC previously not treated with an ALK inhibitor [3]. **Route of administration:** OS **Licensing status** **EU CHMP P.O. date:** 16/12/2021 **FDA M.A. date:** 03/03/2021 **EU Speed Approval Pathway:**No **FDA Speed Approval Pathway:** Yes --- **ABBREVIATIONS:** **AEs**: Adverse Events **ALK:** anaplastic lymphoma kinase **ATP:** adenosine triphosphate **CHMP:** Committee for Medicinal Products for Human Use **CI**: Confidence Interval **EML4:** echinoderm microtubule-associated protein-like 4 **HR**: Hazard Ratio **M.A.:** Marketing Authorization **NSCLC:** non-small cell lung cancer **OS**: Oral Administration **PFS**: Progression free survival **P.O.:** Positive Opinion **Pts:** patients **Q4W**: Every Four Weeks **ROS1**: c-ros oncogene 1 **SAEs**: Serious Adverse Events **Vs**.: Versus	**Summary of clinical EFFICACY:** **CROWN clinical trial (NCT03052608)** is a global, randomized, phase III trial comparing lorlatinib with crizotinib in pts with advanced ALK-positive NSCLC who had notreceived previous systemic treatment for metastatic disease. Pts (n=296) were randomly assigned in 1:1 ratio to receive either oral lorlatinib (n=149) at a dose of 100 mg daily or oral crizotinib (n=147) at a dose of 250 mg twice daily, in cycles of 28 days of treatment. The primary endpoint was PFS. By thecutoff date127 pts had disease progression or died (28% [n=41] in the lorlatinib group vs. 59% [n=86] in the crizotinib group). The percentage of pts alive without disease progression at 12 months was 78% (95% CI, 70-84%) for lorlatinib and 39% (95% CI, 30-45%) for crizotinib(HR 0.28; 95% CI, 0.19-0.41; p<0.001) [4]. **Summary of clinical SAFETY:** AEs of any grade that occurred more frequently (≥10%) with lorlatinib than with crizotinib included hypercholesterolemia (70% vs. 4%), hypertriglyceridemia (64% vs. 6%), edema (55% vs. 39%), increased weight (38% vs. 13%), peripheral neuropathy (34% vs. 15%), cognitive effects (21% vs. 6%), anemia (19% vs. 8%), hypertension (18% vs. 2%), mood effects (16% vs. 5%), and hyperlipidemia (11% vs. 0%). Grade 3-4 AEs occurred in 72% of the pts who received lorlatinib vs. 56% of thosereceiving crizotinib. The most common grade 3-4 AEs in the lorlatinib group were elevated triglyceride levels (20%), increased weight (17%), elevated cholesterol levels (16%), and hypertension (10%). SAEs occurred in 34% of the pts in the lorlatinib arm vs. 27% in the crizotinib arm. Fatal AEs occurred in 14 pts (seven in the lorlatinib group and seven in the crizotinib group) [4]. **Ongoing studies:** ● ***For the same indication:*** Yes ● ***For other indications:*** Yes (only phase II) **Discontinued studies (for the same indication):** No **References:** 1.https://www.ema.europa.eu/en/documents/product-information/lorviqua-epar-product-information_en.pdf 2. https://go.drugbank.com/drugs/DB12130 3.https://www.ema.europa.eu/en/medicines/human/summaries-opinion/lorviqua-0 4. https://pubmed.ncbi.nlm.nih.gov/33207094/ 5. https://gallery.farmadati.it/Home.aspx 6.Jemal A, Bray F, Center MM et al. Global cancer statistics. CA Cancer J Clin 2011; 61: 69–90 7.https://www.pharmastar.it/news/italia/tumore-al-polmone-alk-disponibile-in-italia-lorlatinib-in-regime-di-rimborsabilit-37010 8.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5154547/ 9.https://clinicaltrials.gov/	**Cost of therapy:** in Italy 30 coated tablets of lorlatinib 100 mg cost€4,500.00*[5]. **Ex-factory price* **Epidemiology:** In Europe, lung cancer is estimated to be the second most common cancer and the leading cause of cancer-related mortality, responsible for 388,000 deaths in 2018. NSCLC accounts for 80%-90% of lung cancers [6]. Alterations in the ALK gene are present in 5-7% of pts with NSCLC, with a higher incidence in younger pts (under 50 years of age) [7]. **POSSIBLE PLACE IN THERAPY:** The first-line treatment for ALK positive advanced NSCLC is crizotinib (250mgos/twice/die; q4w). For pts who develop resistance to first-line treatment, additional ALK inhibitors (i.e. alectinib or ceritinib) are recommended [8]. **OTHER INDICATIONS IN DEVELOPMENT:** Yes (lymphoma, solid tumors) [9]. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** - **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Ensartinib, Ceritinib, Brigatinib [9]. *Service reorganization Y/N: No *Possible off label use Y/N: Yes -----

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