Lorlatinib (Lorviqua®) as monotherapy for the treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC)

General information

Drug description [1]	Indication [2]
Lorlatinib (Lorviqua®) is a selective, adenosine triphosphate (ATP)-competitive inhibitor of ALK and c-ros oncogene 1 (ROS1) tyrosine kinases.	Lorlatinib (Lorviqua®) as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor.

Current treatment [3]

- Current first-line treatment options for ALK-positive NSCLC are:
  - Alectinib
  - Ceritinib
  - Crizotinib

Regulatory status

EMA [2]

Approval status for this indication: On 16 December 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Lorviqua®.

The CHMP adopted a new indication as follows:

- Lorviqua® as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor.

✓ **Medicine under additional monitoring**
✓ **Medicine received a conditional marketing authorisation**[1]

Other indications:

- Lorviqua® as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after:
  - alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or
  - crizotinib and at least one other ALK TKI.

FDA [4]

Approval status for this indication: On 3 March 2021, the FDA granted regular approval to lorlatinib (Lorbrena®) for patients with metastatic NSCLC whose tumours are ALK-positive, detected by an FDA-approved test.

- ✓ This application was granted priority review and orphan drug designation.
- ✓ The FDA also approved the Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems, Inc.) as a companion diagnostic for lorlatinib.
- ✓ Lorlatinib received accelerated approval in November 2018 for the second- or third-line treatment of ALK-positive metastatic NSCLC.

Other indications: none

Costs

30 Lorviqua® tablets 100 mg = **€ 4,537.53** (ex-factory price) [5]

Warnings and precautions [6]

- **Risk of serious hepatotoxicity with concomitant use of strong CYP3A**
  - Inducers: Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating Lorbrena®.
- **Central nervous system (CNS) effects**:

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

- CNS effects include seizures, psychotic effects and changes in cognitive function, mood (including suicidal ideation), speech, mental status, and sleep.
- Withhold and resume Lorbrena® at same or reduced dose or permanently discontinue Lorbrena® based on severity.

❖ **Hyperlipidemia:**
- Initiate or increase the dose of lipid-lowering agents.
- Withhold and resume Lorbrena® at same or reduced dose based on severity.

❖ **Atrioventricular block:**
- Withhold and resume Lorbrena® at same or reduced dose based on severity.

❖ **Interstitial lung disease (ILD)/pneumonitis:**
- Immediately withhold Lorbrena® in patients with suspected ILD/pneumonitis.
- Permanently discontinue Lorbrena® for treatment-related ILD/pneumonitis of any severity.

❖ **Hypertension:**
- Monitor blood pressure after 2 weeks and then at least monthly during treatment.
- For severe hypertension, withhold Lorbrena®, then dose reduce or permanently discontinue.

❖ **Hyperglycemia:**
- Assess fasting serum glucose prior to starting Lorbrena® and regularly during treatment.
- If not adequately controlled with optimal medical management, withhold Lorbrena®, then consider dose reduction or permanently discontinue, based on severity.

❖ **Embryo-foetal toxicity:**
- Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus.
- Advise males and females of reproductive potential to use an effective non-hormonal method of contraception.

Additional information [1]

❖ Treatment with lorlatinib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

❖ Detection of ALK-positive NSCLC is necessary for selection of patients for treatment with lorlatinib because these are the only patients for whom benefit has been shown.

❖ Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised. Improper assay performance can lead to unreliable test results.

Study characteristics [7-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CROWN NCT03052608, Study B7461006	296	oral lorlatinib at a dose of 100 mg daily	oral crizotinib at a dose of 250 mg twice daily	PFS as assessed by BICR	**ongoing**[2], global, randomised, phase 3 trial	ALK	Pfizer	[9]

Efficacy (I vs. C); interim analysis data

Patients who had had **disease progression or died** by the time of the data cutoff: 28% vs. 59%

Patients who were **alive without disease progression at 12 months**: 78% (95% CI, 70-84) vs. 39% (95% CI, 30-48); HR 0.28; 95% CI, 0.19-0.41; p<0.001

Patients with PFS at 12 months (as assessed by the investigators): 80% (95% CI, 73-86) vs. 35% (95% CI, 27-43); HR 0.21; 95% CI, 0.14-0.31

OS: NE-NE

Patients with a confirmed objective response as assessed by BICR: 76% (95% CI, 68-83) vs. 58% (95% CI, 49-66)

Safety (I vs. C), interim analysis data

Grade 3 AEs: n= 87/149 (58%) vs. n=67/142 (47%)

Grade 4 AEs: n=21/149 (14%) vs. N=12/142 (8%)

Serious AEs: n=51/149 (34%) vs. n=39/142 (27%)

Fatal AEs: n=7/149 (5%) vs. n=7/142 (5%)

Adverse events leading to treatment discontinuation: n=10/149 (7%) vs. n=13/142 (9%)

[2] The CROWN trial is currently ongoing; estimated study completion date is 02/2024.

Patients with a response that lasted at least 12 months: 70% vs. 27% Patients with measurable or non-measurable **CNS metastases at baseline with a confirmed objective intracranial response** (as assessed by BICR): 66% (95% CI, 49-80) vs. 20% (95% CI, 9-36); **complete intracranial response** in 61% vs. 15% Patients with a **duration of intracranial response of at least 12 months**: 72% vs. 0%. Patients with **measurable CNS metastases at baseline who had an intracranial response** (n=30): 82% (95% CI, 57-96) vs. 23% (95% CI, 5-54); complete response in 71% vs. 8% Patients who **were alive without CNS progression at 12 months**: 96% (95% CI, 91-98) vs. 60% (95% CI, 49-69); HR 0.07; 95% CI 0.03-0.17) **Deaths in the intention-to-treat population at the time of data-cutoff**: 15% vs. 19%; HR for death 0.72 (95% CI, 0.41-1.25); the between-group difference in OS was **not significant.** **Patient-Reported Outcomes** ❖ Mean (±SE) baseline scores in measures of global QoL were 64.6±1.82 in the lorlatinib group and 59.8±1.90 in the crizotinib group. ❖ Patients in the lorlatinib group had a significantly greater overall improvement from baseline in global QoL than those who received crizotinib (estimated mean difference, 4.65; 95% CI, 1.14-8.16), although the difference was not clinically meaningful. ❖ Improvements in QoL were seen as early as cycle 2 and were maintained over time in the lorlatinib group.	

ESMO-MCBS version 1.1 [11]

The ESMO-MSBS can yet not be applied because the median PFS is not available and the OS data is immature (interim analysis).

Risk of bias (RCT) [12]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	-	no, open-label	unclear[3]	yes[4]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ATP= adenosine triphosphate, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, ILD=interstitial lung disease, Int.=intention, MG=median gain, n=number of patients, NE=not estimable, NSCLC=non-small cell lung cancer, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, ROS1= c-ros oncogene 1, SAE=serious adverse event, ST=standard treatment, TKI=tyrosine kinase inhibitor

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[3] The CROWN trial is currently ongoing; interim analysis data available.
[4] The trial was designed by the sponsor and members of the steering committee. Data were collected by the investigators and analysed by the sponsor.

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