PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

LORVIQUA (LORLATINIB)

MARKETING AUTHORIZATION NUMBER 66941

25 mg film-coated tablets

100 mg film-coated tablets

Document Version: 4.0

Document Date: 24 January 2023

Based on Part VI of EU RMP version 5.0, dated 27 April 2022

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
AV	Atrioventricular
CNS	Central Nervous System
CSR	Clinical Study Report
DLP	Data-Lock Point
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
HCP	Healthcare Professionals
HIV	Human immunodeficiency virus
ILD	Interstitial Lung Disease
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	Non Small Cell Lung Cancer
PAES	Post Approval Efficacy Study
PhV	Pharmacovigilance
ROS1	c-ROS Oncogene 1
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics (Europe)
TKI	Tyrosine Kinase Inhibitor

OVERVIEW

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary for lorlatinib is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of lorlatinib in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Pfizer is fully responsible for the accuracy and correctness of the content of the published RMP summary of lorlatinib

SUMMARY OF RISK MANAGEMENT PLAN FOR LORVIQUA

Summary of the risk management plan for Lorviqua (lorlatinib)

This is a summary of the Risk Management Plan (RMP) for Lorviqua. The RMP details important risks of Lorviqua, how these risks can be minimised, and how more information will be obtained about Lorviqua's risks and uncertainties (missing information).

Lorviqua's proposed Summary of Product Characteristics (SmPC) and its package leaflet give essential information to Healthcare Professionals (HCPs) and patients on how Lorviqua should be used.

This summary of the RMP for Lorviqua should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Lorviqua's RMP.

I. The Medicine and What it is Used for

Lorviqua is indicated for adult patients with anaplastic lymphoma kinase (ALK) positive advanced non small cell lung cancer (NSCLC) who have not previously been treated with an ALK inhibitor.

Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non small cell lung cancer (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

Lorviqua is administered orally once a day and is available as film-coated tablets of 25 mg and 100 mg.

Further information about the evaluation of Lorviqua's benefits can be found in Lorviqua's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/lorviqua).

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Lorviqua, together with measures to minimise such risks and the proposed studies for learning more about Lorviqua's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Lorviqua is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Lorviqua are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lorviqua. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

Table 1. List of Important Risks and Missing Information

Important Identified Risks	CNS Effects
	ILD/pneumonitis
Important Potential Risks	AV block
	Pancreatitis
	Embryo-foetal toxicity
Missing Information	Patients with moderate or severe hepatic impairment

II.B. Summary of Important Risks

Table 2. Summary of Important Risks and Missing Information

Important Identified Risk: CNS Effects	
Evidence for linking the risk to the medicine:	Lorviqua non-clinical and clinical studies The relationship between Lorviqua administration and CNS effects has been demonstrated in non-clinical and clinical studies. Temporary discontinuation and dose reduction have been successful in the management of CNS effects.
Risk factors and risk groups:	There are no known risk factors or risk groups for CNS effects following the administration of Lorviqua
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.7, and 4.8 Additional risk minimisation measures: None
Important Identified Risk: ILD/pneumonitis	
Evidence for linking the risk to the medicine:	Lorviqua non-clinical and clinical studies ILD/pneumonitis is a known effect of other ALK/ROS1 inhibitors. However, the relationship between Lorviqua administration and ILD/pneumonitis is not yet established. ILD/pneumonitis can progress to pulmonary fibrosis and other life threatening pulmonary conditions
Risk factors and risk groups:	Risk factors for ILD/pneumonitis include chemotherapy, antibiotics, anti-arrhythmics, and statins. Other contributing factors that may be associated with ILD/pneumonitis include environmental exposures to inhaled asbestos and silicone, infections, and connective tissue disease.
Risk minimisation measures:	Routine risk minimisation measures: SmPC section 4.4, 4.8 Additional risk minimisation measures: None
Important Potential Risk: AV block	
Evidence for linking the risk to the medicine:	Lorviqua non-clinical and clinical studies The relationship between Lorviqua administration and AV block is not yet established. PR interval increase may become symptomatic AV block and in certain cases require placement of pacemaker. If untreated, complete AV block may lead to life threatening or fatal consequences.
Risk factors and risk groups:	Risk factors for AV block include idiopathic fibrosis and sclerosis of the conduction system, ischemic heart disease, drugs (e.g., beta-blockers, calcium channel blockers, digoxin, amiodarone), increased vagal tone, valvulopathy, prior myocardial infarction, valvular abnormalities, cardiac surgery, advanced age, congenital heart, genetic, or other disorder.
Risk minimisation measures:	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 4.8

Table 2. Summary of Important Risks and Missing Information

	Additional risk minimisation measures: None
Important Potential Risk: Pancreatitis	
Evidence for linking the risk to the medicine:	Lorviqua non-clinical and clinical studies Pancreatic enzymes elevation and pancreatitis are known effects of some ALK/ROS1 inhibitors, however the relationship between Lorviqua administration and pancreatitis is not yet established. If untreated, pancreatitis may lead to life threatening or fatal consequences.
Risk factors and risk groups:	Risk factors for pancreatitis include hypertriglyceridaemia, gallstones, heavy alcohol abuse, direct trauma, variety of medications (e.g., steroids, HIV medications, diuretics, anticonvulsants, chemotherapy, antihyperglycemic agents, and atypical antipsychotics), infections such as mumps, smoking, and cystic fibrosis.
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.4, 4.8 Additional risk minimisation measures: None
Important Potential Risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine:	Lorviqua non-clinical and clinical studies Studies in animals treated with Lorviqua and other drugs in class have shown embryo-foetal toxicity, however, the relationship between Lorviqua use and embryo-foetal toxicity has not been established in humans. Lorviqua may cause foetal harm when administered to a pregnant woman.
Risk factors and risk groups:	Risk factors and risk groups include women of childbearing potential, pregnant women, and lactating women.
Risk minimisation measures:	Routine risk minimisation measures: SmPC Sections 4.4, 4.6, 5.3 Additional risk minimisation measures: None
Missing Information: Patients with moderate or severe hepatic impairment	
Risk minimisation measures:	Routine risk minimisation measures: SmPC sections 4.2, 5.2 Additional risk minimisation measures: None
Additional pharmacovigilance activities:	Additional pharmacovigilance activities: Lorviqua Hepatic Impairment Trial (B7461040)

II.C. Post-Authorisation Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

- Study B7461006: A Phase 3, randomized, open label study of lorlatinib (PF-06463922) monotherapy versus crizotinib monotherapy in the first line treatment of patients with advanced ALK positive non small cell lung cancer (B7461006) comparing lorlatinib versus crizotinib in the first line treatment for patients with advanced ALK positive NSCLC to further characterise the efficacy of lorlatinib.

Purpose of the study:
The ongoing study B7461006 will additionally characterize lorlatinib and include overall survival data by 30 June 2025.

- Study short name and title: Study B7461027: Single-arm Study of Lorviqua in patients with advanced ALK positive NSCLC whose disease progressed after one prior second-generation ALK TKI

  Purpose of the study:
  The planned Post Approval Efficacy Study (PAES) will additionally confirm efficacy in the second-line setting i.e. after alectinib or ceritinib.

Both studies will support conversion from the conditional approval to a full marketing authorisation.

II.C.2. Other Studies in Post-Authorisation Development Plan

Lorviqua Hepatic Impairment Trial (B7461040)

Purpose of the study:

The primary objective is to evaluate the effect of moderate and severe hepatic impairment on the 100 mg single dose plasma PK of lorlatinib

The secondary objective is to evaluate the safety and tolerability of a single 100 mg oral dose of lorlatinib in participants with normal hepatic function and participants with moderate or severe hepatic impairment.