SUMMARY OF THE RISK MANAGEMENT PLAN

FOR

LORVIQUA® (LORLATINIB)

25 mg film-coated tablets
100 mg film-coated tablets

This RMP Summary is based on Part VI of the EU RMP for LORVIQUA (lorlatinib) version 1.0, dated 26 February 2019
SUMMARY OF THE RISK MANAGEMENT PLAN FOR LORVIQUA (lorlatinib)

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 of 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 authorized by Swissmedic. Pfizer AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of lorlatinib.

I. The Medicine and What it is Used for

Lorlatinib is authorised to treat adult patients with a kind of advanced lung cancer called non-small cell lung cancer in which there is a specific rearrangement or abnormality in the gene called Anaplastic Lymphoma Kinase or ALK. In addition, patients should have been previously treated with:

- alectinib or ceritinib as the first ALK TKI therapy; or
- crizotinib and at least one other ALK TKI.

Tyrosine kinase inhibitors stop tyrosine kinases from working. Tyrosine kinases are enzymes that are responsible for activating many proteins in the body’s cells causing cancer cells to grow and multiply. The ALK kinases play an important role in the survival and growth of tumour cells, and in the ability of tumour cells to spread to different parts of the body.

Lorlatinib 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 lorlatinib’s benefits can be found in lorlatinib’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

This summary of the RMP for lorlatinib 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 lorlatinib's RMP.
II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of lorlatinib, together with measures to minimise such risks and the proposed studies for learning more about lorlatinib'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 lorlatinib is not yet available, it is listed under ‘missing information’.

II.A. List of Important Risks and Missing Information

Important risks of lorlatinib 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 lorlatinib. 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

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<thead>
<tr>
<th>Important Identified Risks</th>
<th>CNS Effects</th>
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<td>Patients with severe renal impairment</td>
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### 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:** Lorlatinib non-clinical and clinical studies
  - The relationship between lorlatinib 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 lorlatinib

- **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: Interstitial lung disease/pneumonitis**

- **Evidence for linking the risk to the medicine:** Lorlatinib non-clinical and clinical studies
  - ILD/pneumonitis is a known effect of other ALK/ROS1 inhibitors. However, the relationship between lorlatinib 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
  - Additional risk minimisation measures:
    - None

**Important Potential Risk: Atrioventricular block**

- **Evidence for linking the risk to the medicine:** Lorlatinib non-clinical and clinical studies
  - The relationship between lorlatinib administration and atrioventricular 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
### Table 2. Summary of Important Risks and Missing Information

<table>
<thead>
<tr>
<th>Risk minimisation measures:</th>
<th>Routine risk minimisation measures:</th>
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<td>SmPC Sections 4.2, 4.4</td>
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<td>Additional risk minimisation measures:</td>
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<td>None</td>
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#### Important Potential Risk: Pancreatitis

**Evidence for linking the risk to the medicine:**
- Lorlatinib non-clinical and clinical studies
- Pancreatic enzymes elevation and pancreatitis are known effects of some ALK/ROS1 inhibitors, however the relationship between lorlatinib 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 (eg, 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:**
- Lorlatinib non-clinical and clinical studies
- Studies in animals treated with lorlatinib and other drugs in class have shown embryo-foetal toxicity, however, the relationship between lorlatinib use and embryo-foetal toxicity has not been established in humans. Lorlatinib 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:**
- Lorlatinib Hepatic Impairment Trial (B7461009)

#### Missing Information: Patients with severe renal impairment

**Risk minimisation measures:**
- Routine risk minimisation measures:
  - SmPC sections 4.2, 5.2
- Additional risk minimisation measures:
  - None

**Additional pharmacovigilance activities:**
- No additional pharmacovigilance activities
Table 2. Summary of Important Risks and Missing Information

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<tr>
<th>Pharmacovigilance activities:</th>
<th>Lorlatinib Renal Impairment Trial (B7461010)</th>
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II.C. Post-Authorisation Development Plan

Not applicable.

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

The EMA conditional approval in the EU requires completion of 2 studies:

- 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 efficacy and safety of Lorlatinib. This study will demonstrate that single agent lorlatinib is superior to single agent crizotinib in prolonging PFS in ALK-positive NSCLC patients who are treatment naïve.

- The planned Post Approval Efficacy Study (PAES); Single-arm Study of lorlatinib in patients with advanced ALK positive NSCLC whose disease progressed after one prior second-generation ALK TKI 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

Lorlatinib Hepatic Impairment Trial (B7461009)

Purpose of the study:

The primary objective is to evaluate the effect of hepatic impairment on the steady state pharmacokinetics of lorlatinib in advanced cancer patients.

The secondary objectives are:

- To evaluate the effect of hepatic impairment on the safety of lorlatinib in advanced cancer patients.

- To evaluate the antitumor activity of lorlatinib in advanced cancer patients.

Lorlatinib Renal Impairment Trial (B7461010)

Purpose of the study:
The primary objective is to evaluate the effect of renal impairment on the single dose pharmacokinetics of lorlatinib on otherwise healthy subjects.

The secondary objective is to evaluate the safety and tolerability of a single dose of lorlatinib in healthy subjects and subjects with renal impairment.