Public Assessment Report

LORLAK

PRODUCT INFORMATION

Product name	:	LORLAK
Dosage form	:	Film-coated tablet
Active substance	:	Lorlatinib 25 and 100 mg
Pack size	:	Box of 1 blister @ 10 film-coated tablets
MA Holder	:	PT. Pfizer Indonesia, Jakarta
Manufacturer	:	Pfizer Manufacturing Deutschland GmbH, Freiburg, Germany
Registration category	:	New indication and posology
Approved indication	:	*LORLAK® 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 previously treated with one or more ALK tyrosine kinase inhibitors (TKIs)*
Proposed indication	:	*LORLAK as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor*
Proposed posology	:	*The recommended dose schedule of LORLAK is 100 mg taken orally once daily continuously.* *Continue treatment as long as the patient is deriving clinical benefit from therapy.* *LORLAK may be taken with or without food.* *Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. Dose reduction levels are summarized below.* ● *First dose reduction: LORLAK 75 mg taken orally once daily* ● *Second dose reduction: LORLAK 50 mg taken orally once daily* *LORLAK should be permanently discontinued if the patient is unable to tolerate LORLAK 50 mg taken orally once daily. Dose modification recommendations for toxicities and for patients who develop first-degree, second-degree, or complete atrioventricular (AV) block are provided in Table 1 of the approved SPC.*

INTRODUCTION
Lorlak contains the active substance Lorlatinib which is a selective, ATP-competitive, brain-penetrant, small molecule inhibitor of ALK & ROS1 tyrosine kinase, which also inhibits ALK kinase domain mutations responsible for resistance to ALK inhibitor therapy in NSCLC.

As the proposed registration represent a new indication (previously not treated with an ALK inhibitor) and posology addition, the evaluation is currently focused on clinical study data to confirm the efficacy and safety of the drug.

QUALITY ASPECT
N/A
The registration category is new indication and posology addition to the registered drug product. There were no changes to the drug product quality, so no evaluation was carried out on the quality aspect.

EFFICACY AND SAFETY ASPECT
Non-clinical study
N/A

Clinical study
The proposed indication of lorlatinib as monotherapy for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) in adults was supported by multi cohort, single arm phase 1/2 study as well as randomized, open-label phase 3 study, as follows:

1. Administration of lorlatinib 100 mg in ALK treatment-naive patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases (Study B7461001, phase 2 portion, EXP 1 cohort, n=30), showed:
   - Median progression free survival (PFS): 16.6 months (95% CI: 11.8, 28.3)
   - Overall response rate (ORR): 90% (95% CI: 73.5, 97.9); Intracranial ORR: 75% (95% CI: 34.9, 96.8)
   - Median duration of response (DOR): 17.2 months (95% CI: 12.5, 35.1); median intracranial DOR: NE (95% CI: 8.3, NE) months
   - Median time to response (TTR): 1.4 months; median intracranial TTR: 2.1 months
   - Disease control rate (DCR) 12 weeks: 93.3%; Intracranial DCR: 87.5%
   - Median time to progression (TTP): not reached (NR); median intracranial TTP: 11.4 months

2. Administration of lorlatinib 100 mg/day vs. crizotinib 250 mg BID in ALK-treatment naive patients with locally advanced or metastatic ALK-positive NSCLC (Study B7461006, phase 3, n=296), showed:
   - Median PFS: not estimable (NE) vs. 9.3 months (HR: 0.28, 95%CI: 0.19 - 0.41; p<0.0001)
   - Median overall survival (OS): NE on both arms (HR: 0.72, 95%CI: 0.41 - 1.25)
   - ORR: 75.8% vs. 57.8%; Intracranial ORR: 65.8% vs. 20%
   - Median DOR: NE vs. 11 months; Proportion of subjects with DOR ≥ 12 months: 69.9% vs. 27.1%; Intracranial DOR: NE vs. 9.4 months; Proportion of subjects with DOR ≥ 12 months: 72% vs. 0%.
   - Median TTR: 1.8 months vs. 1.8 months
   - Median intracranial-TTP: NE vs. 16.6 months (HR: 0.07, 95% CI: 0.03 - 0.17)

3. Safety aspects showed lorlatinib was well tolerated. ADRs >10% related to lorlatinib were hypercholesterolemia, hypertriglyceridemia, oedema, weight increased, peripheral neuropathy, cognitive effects, hyperlipidemia, anaemia, fatigue, arthralgia, diarrhoea

and mood effects; with SAE grade 5 are respiratory failure, acute cardiac failure, pulmonary embolism, lung malignancy, disease progression, pneumonia, and death.

DECISION
Considering the above efficacy and safety data, it is decided that the registration of indication and posology addition for Lorlak Film-coated Tablet is **approved as per proposed posology and approved the indication with revision, as follows:**

LORLAK as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

Attachment: Lorlak posology changes

Posology and Method of Administration

……

ALK testing

ALK-positive status should be established using a validated ALK assay. 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 utilized. Improper assay performance can lead to unreliable test results.

Recommended dosing

The recommended dose schedule of LORLAK® is 100 mg taken orally once daily continuously. Continue
treatment as long as the patient is deriving clinical benefit from therapy.

LORLAK® may be taken with or without food (see Section 5.2 of the approved SPC).

Patients should be encouraged to take their dose of lorlatinib at approximately the same time each day. Tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

If a dose of lorlatinib is missed, then it should be taken as soon as the patient remembers unless it is less than 4 hours before the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

Dose modifications

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. Dose
reduction levels are summarized below.

- *First dose reduction: LORLAK® 75 mg taken orally once daily*
- *Second dose reduction: LORLAK® 50 mg taken orally once daily*

LORLAK® should be permanently discontinued if the patient is unable to tolerate LORLAK® 50 mg taken orally once daily.
Dose modification recommendations for toxicities and for patients who develop first-degree, second-degree, or complete atrioventricular (AV) block are provided in Table 1 of the approved SPC.

.....

Concurrent use of LORLAK® with strong CYP3A inhibitors may increase lorlatinib plasma concentrations. An alternative concomitant medicinal product with less potential to inhibit CYP3A should be considered (see Sections 4.5 and 5.2 of the approved SPC). If a strong CYP3A inhibitor must be administered concomitantly, the starting LORLAK® dose of 100 mg

once daily should be reduced to once daily 75 mg dose. If concurrent use of a strong CYP3A inhibitor is discontinued, LORLAK® should be resumed at the dose used prior to the initiation of the strong CYP3A inhibitor and after a washout period of 3 to 5 half-lives of the strong CYP3A inhibitor.

Hepatic impairment

No dose adjustments are recommended for patients with mild hepatic impairment. Limited information is
available for lorlatinib in patients with moderate or severe hepatic impairment. Therefore, LORLAK® is not
recommended in patients with moderate to severe hepatic impairment (see Section 5.2 of the approved SPC).

Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment [absolute estimated glomerular filtration rate (eGFR): ≥ 30 mL/min]. A reduced dose of LORLAK® is recommended in patients with severe renal impairment (absolute eGFR < 30 mL/min), e.g. a starting dose of 75 mg taken orally once daily (see Section 5.2 of the approved SPC).

Public Assessment Report

LORLAK

INFORMASI PRODUK

Nama obat	:	LORLAK
Bentuk sediaan	:	Tablet Salut Selaput
Zat aktif	:	Lorlatinib 25 dan 100 mg
Kemasan	:	Dus, 1 blister @ 10 tablet salut selaput
Pendaftar	:	PT. Pfizer Indonesia, Jakarta
Produsen	:	Pfizer Manufacturing Deutschland GmbH, Freiburg, Jerman
Kategori Registrasi	:	Registrasi obat yang sudah terdaftar dengan indikasi dan posologi baru
Indikasi yang disetujui	:	*LORLAK® 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 previously treated with one or more ALK tyrosine kinase inhibitors (TKIs)*
Indikasi yang diajukan	:	*LORLAK as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor*
Posologi yang diajukan	:	*The recommended dose schedule of LORLAK is 100 mg taken orally once daily continuously.* *Continue treatment as long as the patient is deriving clinical benefit from therapy.* *LORLAK may be taken with or without food.* *Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. Dose reduction levels are summarized below.* ● *First dose reduction: LORLAK 75 mg taken orally once daily* ● *Second dose reduction: LORLAK 50 mg taken orally once daily* *LORLAK should be permanently discontinued if the patient is unable to tolerate LORLAK 50 mg taken orally once daily. Dose modification recommendations for toxicities and for patients who develop first-degree, second-degree, or complete atrioventricular (AV) block are provided in Table 1 of approved SPC.*

PENGANTAR

Lorlak mengandung zat aktif Lorlatinib yang *merupakan selective, ATP-competitive, brain-penetrant, small molecule inhibitor of ALK & ROS1 tyrosine kinase*, yang juga menghambat mutasi domain ALK kinase yang bertanggung jawab untuk resistensi terhadap terapi *ALK inhibitor* pada NSCLC.

Mengingat pendaftaran yang diajukan adalah indikasi (untuk pasien yang sebelumnya tidak diobati dengan *ALK inhibitor*) dan posologi baru, saat ini evaluasi difokuskan pada data uji klinik untuk pembuktian efikasi dan keamanan obat lebih lanjut.

ASPEK MUTU

NA

Pengajuan registrasi berupa penambahan indikasi dan posologi baru pada produk obat yang sudah terdaftar. Tidak terdapat perubahan terhadap mutu obat, sehingga tidak dilakukan evaluasi pada aspek mutu

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik

NA

Studi Klinik

Pengajuan indikasi lorlatinib yang diajukan yaitu monoterapi untuk pengobatan *anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)* pada dewasa didukung oleh studi fase 1/2 *multi cohort, single arm* serta studi fase 3 studi dengan desain *random, open label*:

1. Pemberian lorlatinib 100 mg pada pasien *treatment naïve* dengan *advanced ALK-positive NSCLC with or without asymptomatic CNS metastases* (Studi B7461001, fase 2, EXP 1 cohort, n=30), menunjukkan:
    - Median *progression free survival* (PFS): 16,6 bulan (95% CI: 11,8, 28,3)
    - *Overall response rate* (ORR): 90% (95% CI: 73,5, 97,9); ORR intrakranial: 75% (95% CI: 34,9, 96,8)
    - Median *duration of response* (DOR): 17,2 bulan (95% CI: 12,5, 35,1); median DOR intrakranial: NE (95% CI: 8,3, NE) bulan
    - Median *time to response* (TTR): 1,4 bulan; median TTR intrakranial: 2,1 bulan
    - *Disease control rate* (DCR) 12 minggu: 93,3%; DCR intrakranial: 87,5%
    - Median *time to progression* (TTP): not reached (NR); median TTP intrakranial: 11,4 bulan

2. Pemberian lorlatinib 100 mg/hari vs. crizotinib 250 mg BID pada pasien yang belum pernah mendapatkan pengobatan untuk *locally advanced* atau *metastatic ALK-positive NSCLC* (Studi B7461006, fase 3, n=296), menunjukkan:
    - Median PFS: *not estimable* (NE) vs. 9,3 bulan (HR: 0,28, 95%CI: 0,19 – 0,41; p<0.0001)
    - Median *overall survival* (OS): NE pada kedua *arms* (HR: 0,72, 95%CI: 0,41 – 1,25)
    - ORR: 75,8% vs. 57,8%; ORR intrakranial: 65,8% vs 20%
    - Median DOR: NE vs. 11 bulan; proporsi subjek dengan DOR ≥ 12 bulan: 69,9% vs. 27,1%;

DOR intrakranial: NE vs 9,4 bulan; proporsi subjek dengan DOR ≥ 12 bulan: 72% vs. 0%

- Median TTR: 1,8 bulan vs. 1,8 bulan
- Median *intracranial*-TTP: NE vs. 16,6 bulan (HR: 0,07, 95% CI: 0,03 – 0,17)

3. Aspek keamanan menunjukkan lorlatinib dapat ditoleransi dengan baik. ADR >10% terkait lorlatinib adalah hiperkolesterolemia, hipertrigliseridemia, edema, peningkatan berat badan, neuropati perifer, efek kognitif, hiperlipidemia, anemia, kelelahan, artralgia, diare, dan efek *mood* dengan SAE grade 5 adalah gagal napas, gagal jantung akut, emboli paru, keganasan paru, progresi penyakit, pneumonia, dan kematian.

KEPUTUSAN

Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan bahwa registrasi penambahan indikasi dan posologi Lorlak tablet salut selaput **diterima sesuai dengan posologi yang diajukan dan dengan perbaikan indikasi sebagai berikut:**

LORLAK as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

Lampiran : Perubahan Posologi Lorlak

Posology and Method of Administration
……

ALK testing

ALK-positive status should be established using a validated ALK assay. 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 utilized. Improper assay performance can lead to unreliable test results.

Recommended dosing

The recommended dose schedule of LORLAK® is 100 mg taken orally once daily continuously. Continue treatment as long as the patient is deriving clinical benefit from therapy.

LORLAK® may be taken with or without food (see Section 5.2 of the approved SPC).

Patients should be encouraged to take their dose of lorlatinib at approximately the same time each day. Tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

If a dose of lorlatinib is missed, then it should be taken as soon as the patient remembers unless it is less than 4 hours before the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

Dose modifications

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. Dose reduction levels are summarized below.

- *First dose reduction: LORLAK® 75 mg taken orally once daily*
- *Second dose reduction: LORLAK® 50 mg taken orally once daily*

LORLAK® should be permanently discontinued if the patient is unable to tolerate LORLAK® 50 mg taken orally once daily.
Dose modification recommendations for toxicities and for patients who develop first-degree, second-degree, or complete atrioventricular (AV) block are provided in Table 1 of the approved SPC.

.....

Concurrent use of LORLAK® with strong CYP3A inhibitors may increase lorlatinib plasma concentrations. An alternative concomitant medicinal product with less potential to inhibit CYP3A should be considered (see Sections 4.5 and 5.2 of the approved SPC). If a strong CYP3A inhibitor must be administered

concomitantly, the starting LORLAK® dose of 100 mg once daily should be reduced to once daily 75 mg dose. If concurrent use of a strong CYP3A inhibitor is discontinued, LORLAK® should be resumed at the dose used prior to the initiation of the strong CYP3A inhibitor and after a washout period of 3 to 5 half-lives of the strong CYP3A inhibitor.

Hepatic impairment

No dose adjustments are recommended for patients with mild hepatic impairment. Limited information is available for lorlatinib in patients with moderate or severe hepatic impairment. Therefore, LORLAK® is not recommended in patients with moderate to severe hepatic impairment (see Section 5.2 of the approved SPC).

Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment [absolute estimated glomerular filtration rate (eGFR): ≥ 30 mL/min]. A reduced dose of LORLAK® is recommended in patients with severe renal impairment (absolute eGFR < 30 mL/min), e.g. a starting dose of 75 mg taken orally once daily (see Section 5.2 of the approved SPC).