PROFESSIONAL INFORMATION FOR

ERLOCIP Film-Coated Tablets

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ERLOCIP 25 Film-Coated tablets

ERLOCIP 100 Film-Coated tablets

ERLOCIP 150 Film-Coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ERLOCIP 25:

Each film coated tablet contains Erlotinib Hydrochloride equivalent to Erlotinib 25 mg

Contains sugar: lactose monohydrate 17,333 mg

ERLOCIP 100:

Each film coated tablet contains Erlotinib Hydrochloride equivalent to Erlotinib 100 mg

Contains sugar: lactose monohydrate 69,333 mg

ERLOCIP 150:

Each film coated tablet contains Erlotinib Hydrochloride equivalent to Erlotinib 150 mg

Contains sugar: lactose monohydrate 104,000 mg

For the full list of excipients, **see section 6.1**.

3. PHARMACEUTICAL FORM

Film-Coated tablets

ERLOCIP 25: White, round, biconvex film coated tablet debossed with "C1" on one side and plain on the other.

ERLOCIP 100: White, round, biconvex film coated tablet debossed with "C2" on one side and plain on the other.

ERLOCIP 150: White, round, biconvex film coated tablet debossed with "C3" on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Non-Small Cell Lung Cancer (NSCLC)

ERLOCIP is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer with EGFR activating mutation after failure of at least one prior chemotherapy regimen. ERLOCIP was not effective after platinum-based therapy that included gemcitabine.

ERLOCIP monotherapy is indicated for the maintenance treatment of patients having received first-line platinum-based (other than gemcitabine + cisplatin) doublets chemotherapy for locally advanced or metastatic NSCLC.

No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR- negative tumours.

Bronchial Adenocarcinoma

ERLOCIP is indicated for the first-line treatment of patients with locally advanced or metastatic (stage 4) bronchial adenocarcinoma whose tumours have demonstrated EGFR activating mutations and who have never smoked and had ECOG performance status of 0 – 1.

When prescribing ERLOCIP, factors associated with prolonged survival should be taken into account.

No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-negative tumours.

Pancreatic Cancer

ERLOCIP in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

4.2. Posology and method of administration

Posology

ERLOCIP therapy should be supervised by a medical practitioner experienced in anticancer therapies.

Concomitant use of CYP3A4 substrates and modulators may require dose adjustment (see section 4.5). Where dose adjustment is necessary, reduce in 50 mg steps.

Non-Small Cell Lung Cancer and Bronchial Adenocarcinoma:

EGFR mutation testing should be performed prior to initiation of ERLOCIP therapy in chemo-naive patients with advanced or metastatic NSCLC and bronchial adenocarcinoma.

The recommended dose is 150 mg daily taken at least 1 hour before or two hours after the ingestion of food. Where dose adjustment is necessary, reduce in 50 mg steps.

Pancreatic Cancer:

The recommended dose of ERLOCIP is one 100 mg tablet daily taken at least one hour before or two hours after ingestion of food. in combination with gemcitabine (see gemcitabine professional information for pancreatic cancer indication).

Hepatic Impairment*:*

ERLOCIP is eliminated by hepatic metabolism and biliary excretion. Although erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7 to 9)

compared with patients with adequate hepatic function, caution should be used when administering ERLOCIP to patients with hepatic impairment (see **section 5.2**). ERLOCIP should not be used in patients with severe hepatic dysfunction (AST/SGOT and ALT/SGPT > 5 x ULN). Dose reduction or interruption of ERLOCIP should be considered if severe adverse reactions occur. Safety and efficacy have not been studied in patients with severe hepatic dysfunction.

Renal Impairment:

The safety and efficacy of ERLOCIP have not been established in patients with renal impairment **(see section 5.2**). ERLOCIP must not be used in patients with severe renal dysfunction.

Smokers:

Cigarette smoking has been shown to reduce erlotinib exposure by 50 - 60 %. The maximum tolerated dose of ERLOTINIB in NSCLC and bronchial adenocarcinoma patients who currently smoke cigarettes was 300 mg. The 300 mg dose did not show improved efficacy in second line treatment after failure of chemotherapy compared to the recommended 150 mg dose in patients who continue to smoke cigarettes.

Paediatric population:

Safety and efficacy have not been established in patients under the age of 18.

Method of administration:

Oral use.

4.3. Contraindications

Severe hypersensitivity to erlotinib or to any of the excipients listed in **section 6.1**.

4.4. Special warnings and precautions for use

Interstitial Lung Disease:

Patients who are using ERLOCIP in the treatment of non-small cell lung cancer (NSCLC), pancreatic cancer or those with advanced solid tumours have less frequently reported cases of

interstitial lung disease (ILD), including that of fatalities. In the pivotal study BR.21 in NSCLC, the incidence of ILD-like events was (0,8 %) the same in both the placebo and the erlotinib groups.

In the pancreatic cancer study in combination with gemcitabine, the incidence of ILD-like events was 2,5 % in the erlotinib plus gemcitabine group versus 0,4 % in the placebo plus gemcitabine-treated group. The overall incidence in erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0,6 %. Some examples of reported diagnosis in patients suspected of having ILD included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome and lung infiltration. These ILD-like events started from a few days to several months after initiating erlotinib therapy. Most of the cases were associated with confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease or pulmonary infections.

In patients who develop dyspnoea, cough, fever or other acute onsets of progressive pulmonary symptoms while on ERLOCIP, therapy should stop and undergo diagnostic evaluation. Patients treated concurrently with ERLOCIP and gemcitabine should be monitored carefully for the possibility to develop ILD-like toxicity. If ILD is diagnosed, ERLOCIP should be discontinued and the appropriate treatment administered **(see Section 4.8)**

Diarrhoea, Dehydration, Electrolyte Imbalance and Renal Failure:

Diarrhoea (including very rare cases with a fatal outcome) has occurred in approximately 50 % of patients on ERLOCIP and moderate to severe diarrhoea should be treated with e.g. loperamide. In some cases, dose reduction may be necessary. With regards to dehydration associated with severe or persistent vomiting, diarrhoea, anorexia or vomiting, ERLOCIP

therapy should be interrupted, and dehydration should be appropriately treated. Appropriate measures should be taken to treat the dehydration **(see Section 4.8.)**

Patients who are on concomitant chemotherapy present with a fatal risk of hypokalaemia and renal failure secondary to that of dehydration. In more severe or persistent cases of diarrhoea, or cases leading to dehydration, particularly in patients with aggravating risk factors (concomitant medicines, symptoms or diseases or other predisposing conditions including advanced age), ERLOCIP therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patients intravenously. In addition, renal function and serum electrolytes including potassium should be monitored.

Hepatitis, hepatic failure:

Less frequent cases of hepatic failure including that of fatalities have been found during usage of ERLOCIP. Other compounding factors include pre-existing liver disease or concomitant hepatoxic medicine and therefore liver function tests should be considered. Therapy should be interrupted if changes in liver function are severe **(see Section 4.8.)**. ERLOCIP is not recommended for use in patients with severe hepatic dysfunction.

Smokers

Current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced. The degree of reduction is likely to be clinically significant **(see section 4.5**).

Gastrointestinal perforation

Patients receiving ERLOCIP are at an increased risk of developing gastrointestinal perforation, which was observed uncommonly (including some cases with a fatal outcome). Patients receiving concomitant anti-angiogenic medicines, corticosteroids, Non-steroidal Anti-

inflammatory Drugs (NSAIDs), and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. ERLOCIP should be permanently discontinued in patients who develop gastrointestinal perforation **(see section 4.8).**

Ocular disorders

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with ERLOCIP should be interrupted or discontinued.

If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. ERLOCIP should be used with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.

Cases of corneal perforation or ulceration have been reported during use of ERLOCIP (**see section 4.8**). Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with erlotinib treatment which are also risk factors for corneal perforation/ulceration. ERLOCIP therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain.

Bullous and exfoliative skin disorders

Bullous, blistering and exfoliative skin conditions have been reported, including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal **(see section 4.8).** ERLOCIP treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions. Patients with bullous and exfoliative skin disorders should be tested for skin infection and treated according to local management guidelines.

For patients who are exposed to sun, protective clothing, and / or use of sunscreen (e.g. mineral containing) may be advisable.

Smokers:

Current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced. The degree of reduction is likely to be clinically significant (see **sections 4.2, 4.5 and 5.2**).

Interactions with other medicines

Potent inducers of CYP3A4 may reduce the efficacy of erlotinib whereas potent inhibitors of CYP3A4 may lead to increased toxicity. Concomitant treatment with these types of medicines should be avoided (**see section 4.5**).

Other forms of interactions:

Erlotinib is characterised by a decrease in solubility above 5. Medicines that alter pH of the upper gastrointestinal (GI) tract, like proton pump inhibitors, H_2 antagonists and antacids, may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of ERLOCIP when co-administered with such medicines is not likely to compensate for the loss of exposure. Combination of erlotinib with proton pump inhibitors should be avoided. The effects of concomitant administration of erlotinib with H_2 antagonists and antacids are unknown; however, reduced bioavailability is likely. Therefore, concomitant administration of these combinations should be avoided (see **section 4.5**). If the use of antacids is considered necessary during treatment with ERLOCIP, they should be taken at least 4 hours before or 2 hours after the daily dose of ERLOCIP.

Excipients:

ERLOCIP tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ERLOCIP.

4.5. Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

ERLOCIP and CYP substrates:

Erlotinib is a potent inhibitor of CYP1A1. Erlotinib is a moderate inhibitor of CYP3A4 and CYP2C8 as well as a strong inhibitor of glucuronidation by UGT1A1 *in vitro*. The physiological relevance of the strong inhibition of CYP1A1 is unknown due to the very limited expression of CYP1A1 in human tissues.

Erlotinib exposure (AUC) by 39 %, increased significantly when administered with a moderate CYP1A2 inhibitor, ciprofloxacin, while there was no change in the C_{max}. Similarly, the exposure to the active metabolite increased by about 60 % and 48 % for AUC and C_{max}, respectively. Caution should be used when ciprofloxacin or potent CYP1A2 inhibitors such as fluvoxamine are used with ERLOCIP. The clinical relevance of this increase has not been established. Dose reduction of ERLOCIP may be implemented if adverse events related to erlotinib are observed.

When CYP3A4 substrates such as midazolam and erythromycin are co-administered with ERLOCIP, clearance of the substrates is not altered. However, oral bioavailability was decreased by up to 24% for midazolam. In another clinical study, erlotinib was shown not to affect pharmacokinetics of the concomitantly administered CYP3A4/2C8 substrate paclitaxel.

Significant interactions with the clearance of other CYP3A4 substrates are unlikely.

The inhibition of glucuronidation may cause interactions with medicines that are substrates of UGT1A1. Patients with low expression levels of UGT1A1 or genetic glucuronidation disorders

such as Gilberts disease may exhibit increased serum concentrations of bilirubin and must be treated with caution.

Erlotinib is metabolised in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and CYP1B1 in tumour tissue also potentially contribute to the metabolic clearance of erlotinib. Potential interactions may occur with active substances which are metabolised by, or are inhibitors or inducers of, these enzymes.

Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. In a clinical study, the concomitant use of erlotinib with ketoconazole (200 mg orally twice daily for 5 days), a potent CYP3A4 inhibitor, resulted in an increase of erlotinib exposure (86 % of AUC and 69 % of Cmax). Therefore, caution should be used when ERLOCIP is combined with a potent CYP3A4 inhibitor or combined CYP3A4/CYP1A2 inhibitor, e.g. azole antifungals (i.e. ketoconazole, itraconazole, voriconazole), protease inhibitors, erythromycin or clarithromycin. If necessary, the dose of ERLOCIP should be reduced, particularly if toxicity is observed.

Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. In a clinical study, the concomitant use of erlotinib and rifampicin (600 mg orally once daily for 7 days), a potent CYP3A4 inducer, resulted in a 69 % decrease in the median erlotinib AUC, following a 150 mg dose of erlotinib, as compared to erlotinib alone. Pre-treatment and co-administration of rifampicin with a single 450 mg dose of erlotinib resulted in a mean erlotinib exposure (AUC) of 57,5 % of that after a single 150 mg erlotinib dose in the absence of rifampicin treatment. Co-administration of ERLOCIP with CYP3A4 inducers should therefore be avoided. Alternative treatments lacking potent CYP3A4 inducing activity should be considered when possible. For patients who require concomitant treatment with ERLOCIP and a potent CYP3A4 inducer such as rifampicin an increase in dose to 300 mg should be considered while their safety (including renal and liver functions and serum

electrolytes) is closely monitored, and if well tolerated for more than 2 weeks, further increase to 450 mg could be considered with close safety monitoring. Higher doses have not been studied in this setting.

Reduced exposure may also occur with other inducers e.g. phenytoin, carbamazepine, barbiturates or St. John's Wort (hypericum perforatum). Caution should be observed when these medicines are combined with ERLOCIP. Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

ERLOCIP and coumarin-derived anticoagulants:

Concomitant administration of ERLOCIP with anticoagulants such as warfarin and NSAID administration increased International Normalised Ratio (INR) and bleeding events including that of gastrointestinal bleeding **(see section 4.8).** Patients taking warfarin and coumarin-derived anticoagulants should be monitored for changes in both INR and prothrombin time.

ERLOCIP and HMG-CoA reductase inhibitors:

Co-administration of statins with ERLOCIP may less frequently induce myopathy, specifically that of rhabdomyolysis**.**

ERLOCIP and smoking:

Patients who are smoking are encouraged to stop before the beginning of treatment as smoking decreases the level of plasma concentration at 24 hours, as well as significant 2,8-, 1,5- and 9-fold decrease in the AUC_{inf} and C_{max}. The clinical effect of decreased exposure has not been formally addressed but is likely to be clinically significant.

Smokers should be advised to stop smoking as cigarette smoking, which is known to induce CYP1A1 and CYP1A2, has been shown to reduce erlotinib exposure by 50 – 60 % (see sections **4.2, 4.4 and 5.2**).

ERLOCIP and P-glycoprotein inhibitors:

Cyclosporine and verapamil, examples of P-glycoprotein inhibitors, may lead to altered distribution and cause an increased elimination of ERLOCIP since ERLOCIP is a substrate for the P-glycoprotein active transporter. Caution should be maintained despite CNS toxicity and other consequences having not been established.

ERLOCIP and proton pump inhibitors:

Solubility and bioavailability of ERLOCIP may be affected by medicines that alter the pH of the gastro-intestinal tract as erlotinib decreases solubility in a pH of 5. When Erlotinib was administered with a proton pump inhibitor such as omeprazole, both maximum concentration and exposure decreased by 46 % and 61 %, respectively. There was no change to T_{max} or half-life. Therefore, medicines that alter the pH of the upper GI tract may alter the solubility of ERLOCIP and hence its bioavailability. The likelihood of increasing the dose of ERLOCIP to compensate the loss of exposure is minimal. Thus, use of ERLOCIP and a proton pump inhibitor is not advised.

ERLOCIP and antacids:

The use of erlotinib in conjunction with antacids have not been investigated but is likely to impair absorption of ERLOCIP. If the use of antacids in conjunction with ERLOCIP is necessary, then the antacid should be taken 4 hours prior or 2 hours after the dose of ERLOCIP.

If the use of ranitidine is considered, it should be used in a staggered manner, i.e. ERLOCIP must be taken at least 2 hours before or 10 hours after the ranitidine dosing. The ranitidine dose should be divided into 2 equal doses per day.

ERLOCIP and carboplatin/paclitaxel:

There are no pharmacokinetic effects of carboplatin or paclitaxel on ERLOTINIB, however ERLOTINIB can increase platinum concentrations. The co-administrative use of ERLOTINIB with carboplatin or paclitaxel increased the total platinum by 10,6 %.

Although statistically significant, the magnitude of this difference is not considered to be clinically relevant. In clinical practice, there may be other co-factors leading to an increased exposure to carboplatin like renal impairment.

ERLOCIP and capecitabine:

The conjunctive use of ERLOCIP and capecitabine leads to an increase in the exposure of ERLOCIP and a minimal increase in the maximum concentration. Therefore, co-administrative use should be avoided. There are no significant effects of ERLOCIP on the pharmacokinetics of capecitabine.

ERLOCIP and gemcitabine

There were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine.

ERLOCIP and proteasome inhibitors

Due to the working mechanism, proteasome inhibitors including bortezomib may be expected to influence the effect of EGFR inhibitors including erlotinib.

Paediatric population:

Interaction studies have only been performed in adults.

4.6. Fertility, pregnancy and lactation

Women who are pregnant and/or breastfeeding should not take ERLOCIP.

Pregnancy:

There is no significant data that supports the safe use of ERLOCIP in women that are pregnant. Animal studies have concluded an increase in foetal and embryo lethality.

Women of Childbearing Potential

Women of childbearing age should avoid pregnancy whilst on ERLOCIP treatment. Contraceptive methods should be implemented during treatment and two weeks after ERLOCIP treatment is completed.

Breastfeeding:

It is unknown as to whether erlotinib is excreted in breast milk or not. It is recommended that mothers should not breastfeed while on ERLOCIP therapy due to potential harm to the infant.

Fertility:

The potential for human risk is unknown even though animal studies have shown no risk on impaired fertility. However, adverse reactions cannot be ruled out.

4.7. Effects on ability to drive and use machines

ERLOCIP commonly causes keratitis of the eye and uncommonly causes corneal ulceration which may impair vision and hence affect the ability to drive and use machines. ERLOCIP is not associated with impairment of mental ability.

4.8 Undesirable effects

System Organ Class	Frequent	Less frequent
Infections and infestations	Infection[1]	
Metabolism and nutrition disorders	Anorexia, decreased weight	
Psychiatric disorders	Depression	
Nervous system disorders	Headache, neuropathy	
Eye disorders	Keratitis, keratoconjunctivitis sicca, conjunctivitis	Eyelash changes (including in-growing eyelashes, excessive growth and thickening of the eyelashes), corneal ulcerations and perforations[2], uveitis
Respiratory, thoracic and mediastinal disorders	Epistaxis, dyspnoea, cough	Serious interstitial lung disease (ILD), including fatalities
Gastrointestinal dissorders	Diarrhoea[3], nausea, vomiting, stomatitis, abdominal pain, dyspepsia, flatulence.	Gastrointestinal perforations, including fatalities

System Organ Class	Frequent	Less frequent
	Gastrointestinal bleeding4, including fatalities.	
Hepato-biliary disorders	Liver function test abnormalities5 (including increased alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin)	Cases of hepatic failure (including fatalities)[6]
Skin and subcutaneous tissue disorders	Alopecia, paronychia, dry skin, skin fissures, pruritus, rash7 (all grades). Acne, dermatitis acneiform and folliculitis[8].	Hirsutism, eyebrow changes and brittle and loose nails. Mild skin reactions such as hyperpigmentation. Bullous, blistering and exfoliative skin conditions including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which may be fatal.
General disorders and administration site conditions	Fatigue, pyrexia, rigors	

[1]Severe infections, with or without neutropenia, have included pneumonia, sepsis, and cellulitis.

[2]Corneal ulcerations and perforations have been reported very rarely in patients receiving erlotinib as a complication of mucocutaneous inflammation.

[3]Can lead to dehydration, hypokalaemia and renal failure.

[4]Some cases have been associated with concomitant warfarin administration (see section 4.5) and some with concomitant NSAID administration.

[5]These were mainly mild or moderate in severity, transient in nature or associated with liver metastases.

[6]Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications (see **section 4.4)**.

[7]In general, rash manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in sun exposed areas.

[8]Acne, dermatitis acneiform and folliculitis, as mild to moderate and non-serious.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Adverse reactions such as diarrhoea, rash as well as an increase in liver transaminase may occur, in events where patients are exceeding the recommended 150 mg dose. In cases of suspected overdose, ERLOCIP treatment should be withheld, and symptomatic treatment should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agent protein kinase inhibitor, ATC code: L01XE03.

Mechanism of action:

Erlotinib inhibits the intracellular phosphorylation of HER1/EGFR tyrosine kinase (epidermal growth factor receptor type 1, also known as HER1). HER1/EGFR is expressed on the cell surface of normal cells and cancer cells. Erlotinib competitively inhibits ATP binding at the active site of the kinase. *In vitro* studies have shown that inhibition of EGFR phosphotyrosine leads to cell stasis and/or death.

5.2. Pharmacokinetic properties

Absorption:

Oral erlotinib is absorbed after oral administration and should not be taken with food. Erlotinib has an average oral bioavailability of 59 % in comparison to that of IV administration. 95 % of erlotinib is highly bound to plasma proteins after absorption, specifically that of albumin and alpha-1 acid glycoprotein (AAG) with a free fraction of 5 % at recommended dose. After oral administration of a 150 mg dose of erlotinib, at steady state, the median time to reach maximum plasma concentrations is approximately 4,0 hours with median maximum plasma concentrations achieved of 1,995 ng/mL. Prior to the next dose at 24 hours, the median minimum plasma concentrations are 1,238 ng/ml. Median AUC achieved during the dosing interval at steady state are 41,300 µg*hr/mL.

Distribution:

Erlotinib has a mean apparent volume of distribution of 232 L and distributes into tumour tissue of humans. Plasma protein binding is approximately 95 %. In a study of 4 patients (3 with non-small cell lung cancer [NSCLC], and 1 with laryngeal cancer) receiving 150 mg daily oral doses of erlotinib, tumour samples from surgical excisions on Day 9 of treatment revealed tumour concentrations of erlotinib that varied widely but averaged 1,185 ng/g of tissue.

This corresponded to an overall average of 63 % of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumours at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113 % of the observed steady state peak plasma concentrations. Plasma protein binding is approximately 95 %.

Erlotinib binds to serum albumin and alpha-1 acid glycoprotein (AAG).

Biotransformation:

ERLOCIP is metabolised in humans by hepatic cytochrome P450 enzymes. The CYP3A4 is the primary metabolic enzyme, with CYP1A2 being used to a much lesser extent. Extrahepatic metabolism by CYP3A4 in the intestine, CYP1A1 in the lung, and CYP1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib. *In vitro* studies have shown that approximately 80 to 95 % of erlotinib metabolism is by the CYP3A4 enzyme. There are three prime metabolic pathways that are used with ERLOCIP. The first consists of O-demethylation of either side chain, followed by oxidation of the carboxylic acids. The second metabolic pathway is by oxidation of acetylene moiety followed by hydrolysis of the aryl carboxylic acid and lastly, aromatic hydroxylation of the phenyl-acetylene moiety. The primary metabolites of O-demethylation of either side chain have comparable potency to erlotinib in preclinical *in vitro* assays and *in vivo* tumour models. These metabolites are present in levels less than 10 % of erlotinib and portray similar pharmacokinetics as erlotinib.

Elimination:

Erlotinib metabolites and trace amounts of erlotinib are excreted primarily in the faeces (90 %) with a very small amount excreted renally following an oral dose. A population pharmacokinetic analysis showed a mean apparent clearance of 4,47 L/hour with a median half-life of 36,2 hours. The time to reach steady state plasma concentrations was expected to occur in approximately 7 -8 days. There were no significant relationships observed between clearance and patient age, body weight, gender, and ethnicity. Patient factors, which correlate with erlotinib pharmacokinetics are serum total bilirubin, AAG concentrations and smoking. Increased serum concentrations of total bilirubin and AAG were associated with a slower rate of erlotinib clearance. Smokers were associated with a higher clearance of erlotinib.

A second population pharmacokinetic analysis was conducted that incorporated erlotinib data from 204 pancreatic cancer patients who received erlotinib plus gemcitabine. This analysis demonstrated that covariates affecting erlotinib clearance in patients from the pancreatic study were very similar to those seen in the prior single-agent pharmacokinetic analysis. No new covariate effects were identified. Co-administration of gemcitabine had no effect on erlotinib plasma clearance.

Pharmacokinetics in Special populations:

Hepatic Impairments: Primary clearance of erlotinib occurs in the liver. Erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7 – 9) compared with patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases.

Renal Impairments: Erlotinib is not primarily excreted by the kidney as less than 9 % of a single dose is excreted in the urine and there are no data available with patients who have a compromised renal function.

Elderly: No data are available for use in the elderly.

Paediatric: No data are available for use in paediatrics

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:

- Lactose monohydrate,
- Magnesium stearate,
- Microcrystalline cellulose,
- Opadry Complete Film Coating System 20B58900 White,
- Sodium lauryl sulphate, and
- Sodium starch glycolate,

Film coating:

- The film coat is made up of HPMC 2910/ hypromellose, titanium dioxide, hydroxypropyl cellulose and macrogol.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 30 °C.

Store in the original package.

Protect from moisture.

Do not remove blisters from carton until required for use.

6.5. Nature and contents of container

ERLOCIP 25 mg, 100 mg & 150 mg are packed in a clear PVC film/ Plain aluminium blister foil having NC coating with universal heat lacquer packaged in a carton containing 1 blister pack of 10 tablets each or 3 blister packs of 10 tablets each.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD

Building 2,

Junxion Park

10 Elephant Lane,

Century City,

7441

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

ERLOCIP 25: 54/26/0624.621

ERLOCIP 100: 54/26/0625.622

ERLOCIP 150: 54/26/0626.623

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 July 2020

Date of latest renewal: Not applicable

10. DATE OF REVISION OF THE TEXT

11 September 2025