APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

EGROTIB 25, 25 mg, tablets

EGROTIB 100, 100 mg, tablets

EGROTIB 150, 150 mg, tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

<u>EGROTIB 25</u>

Each film-coated tablet contains 25 mg erlotinib (as erlotinib hydrochloride).

<u>EGROTIB 100</u>

Each film-coated tablet contains 100 mg erlotinib (as erlotinib hydrochloride).

<u>EGROTIB 150</u>

Each film-coated tablet contains 150 mg erlotinib (as erlotinib hydrochloride).

<u>Excipients with known effect</u>

Contains sugar, i.e. lactose monohydrate (see section 4.4).

<u>EGROTIB 25</u>

Each 25 mg film-coated tablet contains 16,667 mg lactose monohydrate.

<u>EGROTIB 100</u>

Each 100 mg film-coated tablet contains 66,667 mg lactose monohydrate.

<u>EGROTIB 150</u>

Each 150 mg film-coated tablet contains 100,000 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

EGROTIB 25

White to off white film coated round tablets with 'E' de-bossed on one side and plain on other side.

EGROTIB 100

White to off white film coated round tablets with 'E' de-bossed on one side and '100' on other side.

EGROTIB 150

White to off white film coated round tablets with 'E' de-bossed on one side and '150' on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-Small Cell Lung Cancer (NSCLC)

EGROTIB 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. EGROTIB was not effective after platinum-based therapy that included gemcitabine.

EGROTIB 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

EGROTIB 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 EGROTIB, 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

EGROTIB 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

EGROTIB treatment should be supervised by a medical practitioner experienced in the use of 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 EGROTIB 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 daily dose of EGROTIB is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see gemcitabine professional information for pancreatic cancer indication).

Hepatic impairment: Erlotinib is eliminated by hepatic metabolism and biliary excretion. Although erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7 – 9) compared with patients with adequate hepatic function, caution should be used when administering EGROTIB to patients with hepatic impairment (see section 5.2). EGROTIB should not be used in patients with severe hepatic dysfunction (AST/SGOT and ALT/SGPT > 5 x ULN). Dose reduction or interruption of EGROTIB 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 EGROTIB has not been studied in patients with renal impairment (see section 5.2). EGROTIB should not be used in patients with severe renal impairment.

Smokers: Cigarette smoking has been shown to reduce erlotinib exposure by 50 - 60 %. The maximum tolerated dose of EGROTIB 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 use: The safety and efficacy of EGROTIB has not been established in patients under the age of 18 years.

Method of administration

Oral use.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Interstitial Lung Disease:

Cases of interstitial lung disease (ILD)-like events, including fatalities, have been reported uncommonly in patients receiving erlotinib for treatment of non-small cell lung cancer (NSCLC), pancreatic cancer or other advanced solid tumours. 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 diagnoses in patients suspected of having ILD -like events, included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome, alveolitis 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 acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnoea, cough and fever, EGROTIB therapy should be interrupted pending diagnostic evaluation. Patients treated concurrently with EGROTIB and gemcitabine should be monitored carefully for the possibility to develop ILD-like toxicity. If ILD is diagnosed, EGROTIB should be discontinued and appropriate treatment administered as necessary (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 erlotinib and moderate or severe diarrhoea should be treated, e.g. with loperamide. In some cases dose reduction may be necessary. In the event of severe or persistent diarrhoea, nausea, anorexia, or vomiting associated with dehydration, EGROTIB therapy should be interrupted and appropriate measures should be taken to treat the dehydration (see section 4.8).

There have been reports of hypokalaemia and renal failure (including fatalities). Some reports of renal failure were secondary to severe dehydration due to diarrhoea, vomiting and/or anorexia while others were confounded by concomitant chemotherapy. In more severe or persistent cases of diarrhoea, or cases leading to dehydration, particularly in patients with aggravating risk factors (concomitant medications, symptoms or diseases or other predisposing conditions including advanced age), EGROTIB 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 in patients at risk of dehydration.

Hepatitis, hepatic failure:

Cases of hepatic failure (including fatalities) have been reported during use of erlotinib. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medicines. Therefore, in such patients, periodic liver function testing should be considered. EGROTIB dosing should be interrupted if changes in liver function are severe. EGROTIB is not recommended for use in patients with severe hepatic dysfunction.

Gastrointestinal Perforation:

Patients receiving EGROTIB are at increased risk of developing gastrointestinal perforation (including some cases with a fatal outcome). Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. EGROTIB should be permanently discontinued in patients who develop gastrointestinal perforation.

Bullous and exfoliative skin disorders:

Bullous, blistering and exfoliative skin conditions have been reported, including cases of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal. EGROTIB 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 sun screen (e.g. mineral-containing) may be advisable.

Ocular Disorders:

Cases of corneal perforation or ulceration, uveitis, iridocyclitis and iritis have been

reported during use of erlotinib. 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. EGROTIB therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain.

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 EGROTIB should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.

EGROTIB 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.

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:

Potential 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, H2

antagonists and antacids, may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of EGROTIB 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 H2 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 EGROTIB, they should be taken at least 4 hours before or 2 hours after the daily dose of EGROTIB.

Excipients:

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

In order to improve traceability of biological medicines, the EGROTIB should be clearly recorded in the patient file. Substitution by any other biological medicine requires the consent of the prescribing doctor, and the substitute medicine to be recorded in the files. Information as set forth in this professional information only applies to EGROTIB.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Erlotinib and other CYP substrates

Erlotinib is a potent inhibitor of CYP1A1, and 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.

When erlotinib was co-administered with ciprofloxacin, a moderate CYP1A2 inhibitor, the erlotinib exposure [AUC] increased significantly by 39 %, while no statistically significant change in C_{max} was found. Similarly, the exposure to the active metabolite increased by about 60 % and 48 % for AUC and C_{max}, respectively. The clinical relevance of this increase has not been established. Caution should be exercised when ciprofloxacin or potent CYP1A2 inhibitors (e.g. fluvoxamine) are combined with EGROTIB. If adverse events related to EGROTIB are observed, the dose of EGROTIB may be reduced.

Pre-treatment or co-administration of erlotinib did not alter the clearance of the prototypical CYP3A4 substrates, midazolam and erythromycin, but did appear to decrease the oral bioavailability of midazolam by up to 24 %. 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 therefore unlikely.

The inhibition of glucuronidation may cause interactions with medicines which are substrates of UGT1A1 and exclusively cleared by this pathway. Patients with low expression levels of UGT1A1 or genetic glucuronidation disorders (e.g. Gilbert's 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 C_{max}). Therefore, caution should be used when EGROTIB 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 EGROTIB 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 EGROTIB 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 EGROTIB 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 EGROTIB.

Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

Erlotinib and coumarin-derived anticoagulants

Interaction with coumarin-derived anticoagulants including warfarin leading to increased International Normalized Ratio (INR) and bleeding events, which in some cases were fatal, have been reported in patients receiving erlotinib.

Patients taking coumarin-derived anticoagulants should be monitored regularly for any changes in prothrombin time or INR.

Erlotinib and statins

The combination of EGROTIB and a statin may increase the potential for statin-induced myopathy, including rhabdomyolysis, which was observed rarely.

Erlotinib and smokers

Results of a pharmacokinetic interaction study indicated a significant 2,8-, 1,5- and 9-fold reduced AUC_{inf}, C_{max} and plasma concentration at 24 hours, respectively, after administration of erlotinib in smokers as compared to non-smokers (see section 5.2).

Efficacy in smoking patients has not been established.

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).

Erlotinib and P-glycoprotein inhibitors

Erlotinib is a substrate for the P-glycoprotein active substance transporter. Concomitant administration of inhibitors of Pgp, e.g. ciclosporin and verapamil, may lead to altered distribution and/or altered elimination of EGROTIB. The consequences of this interaction for e.g. CNS toxicity have not been established. Caution should be exercised in such situations.

Erlotinib and medicines altering pH

Erlotinib is characterised by a decrease in solubility at pH above 5. Co-administration of erlotinib with omeprazole, a proton pump inhibitor (PPI), decreased the erlotinib exposure [AUC] and maximum concentration [C_{max}] 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 EGROTIB and hence its bioavailability. Increasing the dose of EGROTIB when co-administered with such medicines is not likely to compensate for this loss of exposure. The effect of antacids and H2 antagonists on the absorption of erlotinib have not been investigated but absorption may be impaired, leading to lower plasma levels. Combination of EGROTIB with proton pump inhibitors should be avoided. The effects of concomitant administration of erlotinib with H2 antagonists and antacids are unknown; however, reduced bioavailability is likely. Therefore, concomitant administration of these combinations should be avoided. If the use of antacids is considered necessary during treatment with EGROTIB, they should be taken at least 4 hours before or 2 hours after the daily dose of EGROTIB.
If the use of ranitidine is considered, it should be used in a staggered manner, i.e. EGROTIB 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.

Erlotinib and Gemcitabine

In a Phase Ib study, there were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine.

Erlotinib and Carboplatin/Paclitaxel

Erlotinib increases platinum concentrations. In a clinical study, the concomitant use of erlotinib with carboplatin and paclitaxel led to an increase of total platinum AUC_{0-48} of 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. There were no significant effects of carboplatin or paclitaxel on the pharmacokinetics of erlotinib.

Erlotinib and Capecitabine

Capecitabine may increase EGROTIB concentrations. When erlotinib was given in combination with capecitabine, there was a statistically significant increase in erlotinib AUC and a borderline increase in C_{max} when compared with values observed in another study in which erlotinib was given as single agent. There were no significant effects of erlotinib on the pharmacokinetics of capecitabine.

Erlotinib and proteasome inhibitors

Due to the working mechanism, proteasome inhibitors including bortezomib may be expected to influence the effect of EGFR inhibitors including EGROTIB. Such influence is supported by limited clinical data and preclinical studies showing EGFR degradation through the proteasome.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must be advised to avoid pregnancy while on

EGROTIB. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy. Women who are pregnant and/or breastfeeding should not receive EGROTIB.

Pregnancy

There are no studies in pregnant and/or breastfeeding women using EGROTIB. Studies in animals have shown no evidence of teratogenicity or abnormal parturition. However, an adverse effect on the pregnancy can not be excluded as rat and rabbit studies have shown increased embryo/foetal lethality. The potential risk for humans is unknown.

Breastfeeding

It is not known whether erlotinib is excreted in human milk. No studies have been conducted to assess the impact of EGROTIB on milk production or its presence in breast milk. As the potential harm to the nursing infant is unknown, mothers should be advised against breastfeeding while receiving EGROTIB and for at least 2 weeks after the final dose.

Fertility

Studies in animals have shown no evidence of impaired fertility. However, an adverse effect on the fertility can not be excluded as animal studies have shown effects on reproductive parameters. The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed, however, EGROTIB is not associated with impairment of mental ability.

4.8 Undesirable effects

Tabulated list of adverse reactions

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	Diarrhoea[3], nausea,	Gastrointestinal

disorders	vomiting, stomatitis, abdominal pain, dyspepsia, flatulence. Gastrointestinal bleeding[4], including fatalities.	perforations, including fatalities
Hepato-biliary disorders	Liver function test abnormalities[5] (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, rash[7] (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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Single oral doses of erlotinib up to 1 000 mg in healthy subjects, and up to 1 600 mg (given as a single dose once weekly) in cancer patients have been tolerated. Repeated twice daily doses of 200 mg in healthy subjects were poorly tolerated after only a few days of dosing. Based on the data from these studies, severe adverse events such as diarrhoea, rash and possibly liver transaminase elevation may occur above the recommended dose. In case of suspected overdose EGROTIB should be withheld and symptomatic treatment initiated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action:

Erlotinib inhibits the intracellular phosphorylation of HER1/EGFR (epidermal growth factor receptor type 1, also known as HER1). HER1/EGFR is expressed on the cell surface of normal cells and cancer cells. In non-clinical models, inhibition of EGFR phosphotyrosine results in cell stasis and/or death.

5.2 Pharmacokinetic properties

Absorption:

Oral erlotinib is absorbed after oral administration and has an extended absorption phase, with mean peak plasma levels occurring at approximately 4 hours after oral dosing. A study in normal healthy volunteers provided an estimate oral bioavailability of 59 % compared to IV administration. The exposure after an oral dose may be increased by food. Following absorption, erlotinib is highly bound in blood, with approximately 95 % bound to blood components, primarily to plasma proteins (i.e. albumin and alpha-1 acid glycoprotein [AAG]), with a free fraction of

approximately 5 % at the recommended dose. Following a 150 mg oral 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. Erlotinib distributes into tumour tissue of humans. 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:

Erlotinib is metabolised in humans by hepatic cytochrome P450 enzymes, primarily CYP3A4, and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in the intestine, CYP1A1 in lung and CYP1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib. *In vitro* studies indicate approximately 80 – 95 % of erlotinib metabolism is by the CYP3A4 enzyme. There

are three main metabolic pathways identified:

1) O-demethylation of either side chain or both, followed by oxidation to the carboxylic acids;

2) oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid; and

3) aromatic hydroxylation of the phenyl-acetylene moiety.

The primary metabolites of erlotinib produced by O-demethylation of either side chain have comparable potency to erlotinib in preclinical *in vitro* assays and *in vivo* tumour models. They are present at levels that are less than 10 % of erlotinib and display similar pharmacokinetics as erlotinib.

Elimination:

The metabolites and trace amounts of erlotinib are excreted predominantly via the faeces (more than 90 %), with renal elimination accounting for only a small amount of an oral dose.

A population pharmacokinetic analysis in 591 patients receiving single agent erlotinib show a mean apparent clearance of 4,47 L/hour with a median half-life of 36,2 hours. Therefore, the time to reach steady state plasma concentration would be expected to occur in approximately 7 – 8 days. No significant relationships between predicted apparent clearance and patient age, body weight, gender, and ethnicity were observed.

Patient factors, which correlate with erlotinib pharmacokinetics, are serum total bilirubin, AAG concentrations and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a slower rate of erlotinib clearance; however, smokers had a higher rate of erlotinib clearance.

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:

There have been no specific studies in paediatric or elderly patients.

Hepatic impairment:

Erlotinib is mainly cleared by 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 impairment:

Erlotinib and its metabolites are not significantly excreted by the kidneys, as less than 9 % of a single dose is excreted in the urine. No clinical studies have been conducted in patients with compromised renal function.

Smokers:

A pharmacokinetic study in nonsmoking and currently cigarette smoking healthy subjects has shown that cigarette smoking leads to increased clearance of, and decreased exposure to, erlotinib. The $AUC_{0\text{-infinity}}$ in smokers was about 1/3 of that in never/former smokers (n = 16 in each of smoker and never/former smoker arms). This reduced exposure in current smokers is presumably due to induction of CYP1A1 in lung and CYP1A2 in the liver.

In the pivotal Phase III NSCLC trial, current smokers achieved erlotinib steady state trough plasma concentration of 0,65 µg/mL (n = 16) which was approximately 2-fold less than the former smokers or patients who had never smoked (1,28 µg/mL, n = 108). This effect was accompanied by a 24 % increase in apparent erlotinib plasma clearance.

In a phase I dose escalation study in NSCLC patients who were current smokers, pharmacokinetic analyses at steady-state indicated a dose proportional increase in erlotinib exposure when the erlotinib dose was increased from 150 mg to the maximum tolerated dose of 300 mg. Steady-state trough plasma concentrations at a 300 mg dose in current smokers in this study was 1,22 µg/mL (n = 17).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium lauryl sulphate

Sodium starch glycolate Type A

Tablet coat

Hydroxypropyl cellulose (E463)

Hypromellose (E464)

Macrogol

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 ºC.

Keep in the outer carton until required for use.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

EGROTIB 25 mg: Alu/PVC blisters containing 30 tablets per pack

EGROTIB 100 mg: Alu/PVC blisters containing 30 tablets per pack

EGROTIB 150 mg: Alu/PVC blisters containing 30 tablets per pack Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd

Block B, 204 Rivonia Road,

Morningside,

Sandton,

2057

8 REGISTRATION NUMBER(S)

EGROTIB 25: 56/26/0128

EGROTIB 100: 56/26/0129

EGROTIB 150: 56/26/0130

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 June 2023

10 DATE OF REVISION OF TEXT

Not applicable.