Applicant : Eurolab (Pty) Ltd
Proprietary name : Tarpib 25 mg & 100 mg & 150 mg
Dosage form and strength : Film-coated tablets 25 mg & 100 mg & 150 mg
Date of submission : 12 February 2025
Approval date : 23 May 2025

Approved Professional Information for Medicines for Human Use

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

TARPIB 25 mg (25 mg, film-coated tablets)

TARPIB 100 mg (100 mg, film-coated tablets)

TARPIB 150 mg (150 mg, film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of **TARPIB 25 mg** contains erlotinib hydrochloride equivalent to 25 mg erlotinib.

Contains sugar: Lactose monohydrate 23,98 mg

Each film-coated tablet of **TARPIB 100 mg** tablets contains erlotinib hydrochloride equivalent to 100 mg erlotinib.

Contains sugar: Lactose monohydrate 95,93 mg

Each film-coated tablet of **TARPIB 150 mg** tablets contains erlotinib hydrochloride equivalent to 150 mg erlotinib.

Contains sugar: Lactose monohydrate 143,90 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

TARPIB 25 MG tablets: White to yellowish, round biconvex, film-coated tablet, engraved with "25" on one side.

TARPIB 100 mg tablets: White to yellowish, round biconvex, film-coated tablet, engraved with "100" on one side.

T**ARPIB 150 mg tablets:** White to yellowish, round biconvex, film-coated tablet, engraved with "150" on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TARPIB is indicated for:

- **Non-small cell lung cancer (NSCLC):**

In patients with locally advanced or metastatic non-small cell lung cancer with EGFR (epidermal growth factor receptor type 1, also known as HER1) activating mutation after failure of at least one prior chemotherapy regimen. **TARPIB** was not effective after platinum-based therapy that included gemcitabine.

TARPIB 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 (see section 5.1. Mechanism of action).

- **Bronchial adenocarcinoma:**

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 to 1.

When prescribing **TARPIB**, 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 (see section 5.1. Mechanism of action).

TARPIB in combination with gemcitabine is indicated for:

- **Pancreatic cancer**

The first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer.

4.2. Posology and method of administration

Posology

Adults:

TARPIB 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:

EGFR mutation testing should be performed prior to initiation of **TARPIB** 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 **TARPIB** is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the professional information of gemcitabine for the recommended dose).

Special populations

Hepatic impairment

TARPIB is eliminated by hepatic metabolism and biliary excretion. Although erlotinib, as contained in **TARPIB**, exposure is 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 **TARPIB** to patients with hepatic impairment (see section 5.2). **TARPIB** should not be used in patients with severe hepatic dysfunction (AST/SGOT and ALT/SGPT > 5 x ULN) (see section 4.3). Dose reduction or interruption of **TARPIB** 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 **TARPIB** has not been studied in patients with renal impairment (see section 5.2). **TARPIB** should not be used in patients with severe renal impairment.

Smokers

Cigarette smoking reduces erlotinib, as contained in **TARPIB**, exposure by 50 % to 60 %. The maximum tolerated dose of **TARPIB** in NSCLC and bronchial adenocarcinoma patients who currently smoke cigarettes is 300 mg. The 300 mg dose does 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 (see section 5.2).

Paediatric population

The safety and efficacy of **TARPIB** has not been established in patients under the age of 18 years (see section 4.4).

Method of administration

TARPIB should be taken at least one hour before or two hours after the ingestion of food (see section 5.2).

4.3. Contraindications

TARPIB is contraindicated in:

- Patients with hypersensitivity to erlotinib or to any excipients in **TARPIB** (see section 6.1).

4.4. Special warnings and precautions for use

Interstitial lung disease (ILD)

Cases of interstitial lung disease (ILD)-like events, including fatalities, have been reported uncommonly in patients receiving **TARPIB** for treatment of non-small cell lung cancer (NSCLC), pancreatic cancer or other advanced solid tumours.

Studies conducted in NSCLC showed the incidence of ILD-like events was (0,8 %) the same in both the placebo and the erlotinib, as contained in **TARPIB**, groups.

In pancreatic cancer studies 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) was 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, **TARPIB** therapy should be interrupted pending diagnostic evaluation.

Patients treated concurrently with erlotinib and gemcitabine should be monitored carefully for the possibility to develop ILD-like toxicity.

If ILD is diagnosed, **TARPIB** should be discontinued and appropriate treatment administered as necessary (see section 4.8).

Diarrhoea, dehydration, electrolyte imbalance and renal failure

Diarrhoea has occurred in approximately 50 % of patients on **TARPIB** 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, **TARPIB** 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), **TARPIB** 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

Serious cases of medicine induced liver injury (DILI) including hepatitis, acute hepatitis and hepatic failure (including fatalities) have been reported during use of **TARPIB**. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medicines. Therefore, in such patients, periodic liver function testing should be considered. The frequency of monitoring of liver function should be increased in patients with pre-existing hepatic impairment or biliary obstruction. Prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury. **TARPIB** dosing should be interrupted if changes in liver function are severe (see section 4.8). **TARPIB** is not recommended for use in patients with severe hepatic dysfunction.

Gastrointestinal perforation

Patients receiving **TARPIB** are at increased risk of developing gastrointestinal perforation (including some cases with a fatal outcome). Patients receiving concomitant anti-angiogenic medicine, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. **TARPIB** 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 (see section 4.8). **TARPIB** treatment should be interrupted or discontinued if the patient develops severe bullous, blistering, or exfoliating conditions.

Ocular disorders

Cases of corneal perforation or ulceration, uveitis, iridocyclitis and iritis have been reported during use of **TARPIB** (see section 4.8).

Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with **TARPIB** treatment which are also risk factors for corneal perforation/ulceration.

TARPIB 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 **TARPIB** should be interrupted or discontinued.

If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. **TARPIB** 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

Efficacy in smoking or previous or past-smoking patients has not been established.

Current smokers should be advised to stop smoking, as plasma concentrations of erlotinib, as contained in **TARPIB**, 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, 5.2).

Assessment of EGFR mutation status

When considering the use of **TARPIB** as a first line or maintenance treatment for locally advanced or metastatic NSCLC, it is important that the EGFR mutation status of a patient is determined.

A validated, robust, reliable and sensitive test with a prespecified positivity threshold and demonstrated utility for the determination of EGFR mutation status, using either tumour DNA derived from a tissue sample or circulating free DNA (cfDNA) obtained from a blood (plasma) sample, should be performed according to local medical practice.

If a plasma-based cfDNA test is used and the result is negative for activating mutations, perform a tissue test wherever possible due to the potential for false negative results from a plasma-based test.

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, as contained in **TARPIB**, is characterised by a decrease in solubility at pH above 5. Medicines that alter the pH of the upper gastrointestinal (GI) tract, like proton pump inhibitors, H_2 antagonists and antacids, may alter the solubility of erlotinib, as contained in **TARPIB**, and hence its bioavailability. Increasing the dose of **TARPIB** when co-administered with such medicines is not likely to compensate for the loss of exposure.

Combination of **TARPIB** with proton pump inhibitors should be avoided. The effects of concomitant administration of **TARPIB** 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 **TARPIB**, they should be taken at least 4 hours before or 2 hours after the daily dose of **TARPIB**.

TARPIB contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **TARPIB**.

4.5. Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Other CYP substrates

Erlotinib, as contained in **TARPIB**, 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, as contained in **TARPIB**, 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 **TARPIB**. If adverse events related to **TARPIB** are observed, the dose of **TARPIB** may be reduced.

Pre-treatment or co-administration of **TARPIB** 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, as contained in **TARPIB**, 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, as contained in **TARPIB**, 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 erlotinib 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 erlotinib should be reduced, particularly if toxicity is observed.

Potent inducers of CYP3A4 activity increase erlotinib, as contained in **TARPIB**, metabolism and significantly decrease erlotinib plasma concentrations. In a clinical study, the concomitant use of erlotinib, as contained in **TARPIB**, 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 **TARPIB**, as compared to **TARPIB** alone. Pre-treatment and co- administration of rifampicin with a single 450 mg dose of **TARPIB** resulted in a mean erlotinib exposure (AUC) of 57,5 % of that after a single 150 mg **TARPIB** dose in the absence of rifampicin treatment. Co-

administration of **TARPIB** 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 **TARPIB** 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 active substances are combined with erlotinib. Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

Anticoagulants

Interactions with warfarin, leading to increased International Normalised Ratio (INR) and bleeding events, which in some cases were fatal have been reported in patients receiving **TARPIB**. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

Statins

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

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 **TARPIB** in smokers as compared to non-smokers.

Efficacy in smoking patients has not been established.

Smokers should be advised to stop smoking a cigarette smoking, which is known to induce CYP1A1 and CYP1A2, has been shown to reduce erlotinib exposure by 50 % to 60 %.

P-glycoprotein inhibitors

Erlotinib, as contained in **TARPIB**, 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 erlotinib. The consequences of this interaction for e.g. CNS toxicity have not been established. Caution should be exercised in such situations.

Medicines altering pH

Erlotinib, as contained in **TARPIB**, is characterised by a decrease in solubility at pH above 5. Studies have shown that co-administration of **TARPIB** 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 gastrointestinal (GI) tract may alter the solubility of **TARPIB** and hence its bioavailability.

Increasing the dose of **TARPIB** when co-administered with such medicines is not likely to compensate for this loss of exposure. The effect of antacids and H_2 antagonists on the absorption of erlotinib, as contained in **TARPIB**, have not been investigated but absorption may be impaired, leading to lower plasma levels. Combination of **TARPIB** 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.

If the use of antacids is considered necessary during treatment with **TARPIB**, they should be taken at least 4 hours before or 2 hours after the daily dose of **TARPIB**. If the use of ranitidine is considered, it should be used in a staggered manner, i.e. erlotinib 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.

Gemcitabine

Studies have shown there were no significant effects of gemcitabine on the pharmacokinetics of erlotinib, as contained in **TARPIB**, nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine.

Carboplatin/Paclitaxel

TARPIB increases platinum concentrations. In a clinical study, the concomitant use of erlotinib, as contained in **TARPIB**, 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.

Capecitabine

Capecitabine may increase **TARPIB** concentrations. When **TARPIB** 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 **TARPIB** was given as single medicine. There were no significant effects of **TARPIB** on the pharmacokinetics of capecitabine.

Proteasome inhibitors

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

4.6. Fertility, pregnancy and lactation

Women who are pregnant or breastfeeding should not receive **TARPIB**. There are no studies in pregnant and/or breastfeeding women using **TARPIB**.

Women of childbearing potential / Contraception in males and females

Male patients taking **TARPIB** should be advised to use highly effective contraception, until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites plus an additional 4 months after exposure (i.e. five half-lives after the last dose, plus 60-75 days for sperm production plus 10-14 days for the transport to epididymis).

Female patients and female sexual partners of male patients taking **TARPIB**, should be advised to use highly effective contraception, until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites plus an additional 7 months after the exposure (i.e. five half-lives after the last dose plus 6 months which covers the growth and maturation phase of folliculogenesis).

Pregnancy

There are no studies for the use of **TARPIB** in pregnant women. Studies in animals have shown reproductive toxicity.

Breastfeeding

There are no studies for the use of **TARPIB** in breastfeeding women.

As the potential for harm to the nursing infant is unknown, mothers should be advised against breastfeeding while receiving **TARPIB** 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 cannot 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. **TARPIB** is not associated with impairment of mental ability.

4.8. Undesirable effects

a) Summary of the safety profile

Non-small cell lung cancer (**TARPIB** administered as monotherapy)

Studies assessing the safety of **TARPIB** for first-line or maintenance treatment of NSCLC patients with EGFR activating mutations have shown that rash and diarrhoea were the most frequent effects. Dose modifications (interruptions or reductions) for rash and diarrhoea were required.

In general, rash manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in sun exposed areas. For patients who are exposed to sun, protective clothing, and/or use of sunscreen (e.g. mineral containing) may be advisable.

Pancreatic cancer (**TARPIB** administered concurrently with gemcitabine)

The most common adverse reactions in studies in pancreatic cancer patients receiving **TARPIB** plus gemcitabine were fatigue, rash and diarrhoea. Rash and diarrhoea each resulted in dose reductions in 2 % of the patients.

b) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations	Severe infections, with or without neutropenia has included pneumonia, sepsis, and cellulitis.		
Metabolism and	Anorexia, weight		

nutrition disorders	decreased		
Eye disorders	Keratoconjunctivitis sicca, conjunctivitis, keratitis	Eyelash changes including in-growing eyelashes, excessive growth, thickening of eyelashes, corneal ulcerations, corneal perforations, uveitis	
Psychiatric disorders	Depression		
Nervous system disorders	Neuropathy, headache		
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough, epistaxis	Interstitial lung disease including fatalities	
Gastrointestinal disorders	Diarrhoea which can lead to dehydration, hypokalaemia and renal failure, nausea, vomiting, stomatitis, abdominal pain, dyspepsia, flatulence, gastrointestinal bleeding including fatalities[1]	Gastrointestinal perforations including fatalities, pneumatosis intestinalis	

Hepatobiliary disorders	Liver function test abnormalities, increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin	Hepatic failure including fatalities[2], hepatitis	Acute hepatitis
Skin and subcutaneous tissue disorders	Rash (mild tomoderate), pruritus, dry skin, alopecia, paronychia, folliculitis, acne, dermatitis acneiform, Skin fissures	Hirsutism, eyebrow changes, brittle and loose nails, mild skin reactions such as hyperpigmentation, bullous, blistering, and exfoliative skin conditions including suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis which may be fatal, palmar plantar erythrodysaesthesia syndrome	
General disorders and administration	Fatigue, pyrexia, rigors		

site conditions			
Renal and urinary disorders	Renal insufficiency	Nephritis, proteinuria	

[1] Some cases have been associated with concomitant warfarin administration and some with concomitant NSAID administration.

[2] Confounding factors included pre-existing liver disease or concomitant hepatotoxic medicines.

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. Healthcare providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website, or to Eurolab (Pty) Ltd. by email: drug-safety@eurolab.co.za. By reporting side effects, you can help provide more information on the safety of **TARPIB**.

4.9. Overdose

Symptoms

Single oral doses of **TARPIB** up to 1 000 mg in healthy subjects, and up to 1 600 mg in given as a single dose once weekly 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.

Treatment

In case of suspected overdose **TARPIB** should be withheld and symptomatic treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A 26 Cytostatic agents

Pharmacotherapeutic group: antineoplastic agent protein kinase inhibitor ATC code: L01XE03

Mechanism of action

Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor.

Erlotinib inhibits the intracellular phosphorylation of EGFR. 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 % to 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 **TARPIB** 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 to 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.

Special populations

Based on population pharmacokinetic analysis, no clinically significant relationship between predicted apparent clearance and patient age, bodyweight, gender, and ethnicity were observed. Patient factors, which correlated with erlotinib pharmacokinetics, were serum total bilirubin, AAG and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a reduced erlotinib clearance. The clinical relevance of these differences is unclear.

Smokers

A pharmacokinetic study in non-smoking 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 **TARPIB** 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).

Paediatric and elderly population

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 to 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 kidney, 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate, macrogol 3350 (E1521), magnesium stearate (E470b), methacrylic acid - ethyl acrylate copolymer (1:1) Type A, microcrystalline cellulose (E460), polyvinyl alcohol (E1203), sodium hydrogen carbonate, sodium starch glycolate Type A, talc (E553b), titanium dioxide (E171).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

48 months.

6.4. Special precautions for storage

Store at or below 25 °C.

6.5. Nature and contents of container

10 film-coated tablets are packed in silver Aluminium-OPA/Alu/PVC blister strips and 3 blister strips are packed into an outer cardboard carton.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park,

3 Stirrup Lane, Van Reenens Avenue,

Woodmead,

2144

8. REGISTRATION NUMBERS

TARPIB 25 mg: A 52/26/0773

TARPIB 100 mg: A 52/26/0774

TARPIB 150 mg: A 52/26/0775

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

05 May 2020

10. DATE OF REVISION OF TEXT

23 May 2025