PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

25 film-coated tablets

TYREC 100 film-coated tablets

TYREC 150 film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TYREC 25 film-coated tablet contains 27,3 mg erlotinib hydrochloride equivalent to 25 mg of erlotinib.

Contains sugar: 17,5 mg lactose monohydrate per film-coated tablet.

Each TYREC 100 film-coated tablet contains 109,3 mg erlotinib hydrochloride equivalent to 100 mg of erlotinib.

Contains sugar: 70 mg lactose monohydrate per film-coated tablet.

Each TYREC 150 mg film-coated tablet contains 163,9 mg erlotinib hydrochloride equivalent to 150 mg of erlotinib.

Contains sugar: 105 mg lactose monohydrate per film-coated tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.

TYREC 25: White to off white round, biconvex, film-coated tablets, debossed with "S13" on one side and plain on other side.

TYREC 100: White to off white round, biconvex, film-coated tablets, debossed with "S12" on one side and plain on other side.

TYREC 150: White to off white round, biconvex, film-coated tablets, debossed with

"S11" on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-small cell lung cancer (NSCLC)

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

TYREC 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).

Bronchial adenocarcinoma

TYREC 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 Eastern Cooperative Oncology Group (ECOG) performance status of 0 – 1.

When prescribing TYREC, factors associated with prolonged survival should be considered. No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-negative tumours (see section 5.1).

Pancreatic cancer

TYREC 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

TYREC 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.

Posology

Non-small cell lung cancer and bronchial adenocarcinoma

EGFR mutation testing should be performed prior to initiation of TYREC 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 TYREC 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).

Special populations

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 TYREC to patients with hepatic impairment (see section 5.2). TYREC should not be used in patients with severe hepatic dysfunction (AST/SGOT and ALT/SGPT > 5 x ULN). Dose reduction or

interruption of TYREC 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 TYREC has not been studied in patients with renal impairment, (see section 5.2). Use of TYREC with severe renal impairment is not recommended.

Smokers

Cigarette smoking has been shown to reduce erlotinib exposure by 50 - 60 %. The maximum tolerated dose of TYREC in NSCLC and bronchial adenocarcinoma patients who currently smoke cigarettes were 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

The safety and efficacy of TYREC in patients under the age of 18 years. has not been established.

Method of administration

For oral use.

TYREC treatment should be supervised by a medical practitioner experienced in the use of anticancer therapies.

4.3 Contraindications

- Hypersensitivity to erlotinib or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

When considering the use of erlotinib as in TYREC 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.

Interstitial lung disease

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

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 (ARDS), alveolitis and lung infiltration. In most cases, confounding or contributing factors, such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease or pulmonary infections, were associated with these ILD-like events.

TYREC therapy should be interrupted, in patients who develop acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnoea, cough and fever, pending diagnostic evaluation. TYREC therapy should be discontinued, and

appropriate treatment administered as necessary, if ILD is diagnosed, (see section 4.8).

Diarrhoea, dehydration, electrolyte imbalance and renal failure

Diarrhoea has occurred in patients on erlotinib as in TYREC therapy, and in some cases, dose reduction may be necessary. Moderate or severe diarrhoea should be treated, e.g. with loperamide.

In the event of severe or persistent diarrhoea, nausea, anorexia, or vomiting associated with dehydration, TYREC 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 cases 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), TYREC 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

Erlotinib as in TYREC is not recommended for use in patients with severe hepatic dysfunction. [2] Cases of hepatic failure (including fatalities) have been reported during use of TYREC. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medicines, therefore, in such patients, periodic liver function testing should be considered. TYREC dosing should be interrupted if changes in liver function are severe.

Gastrointestinal perforation

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

For patients who are exposed to sun, protective clothing, and/or use of sunscreen may be advisable.

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, or if patients present with acute/worsening ocular disorders such as eye pain, treatment with erlotinib should be interrupted or discontinued. Erlotinib as in TYREC should be used with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eyes. Contact lens use is also a risk factor for keratitis and ulceration. Cases of corneal perforation or ulceration, uveitis, iridocyclitis and iritis have been reported during use of erlotinib as in TYREC (see section 4.8). Other risk factors for corneal perforation/ulceration, such as other ocular disorders, including abnormal eyelash

growth, keratoconjunctivitis sicca or keratitis have been observed with TYREC treatment.

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, 5.1 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 as in TYREC is characterised by a decrease in solubility above 5. Medicines that alter the pH of the upper gastrointestinal tract (GI) tract, like proton pump inhibitors, H2 antagonists and antacids, may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of TYREC, 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 TYREC, they should be taken at least 4 hours before or 2 hours after the daily dose of TYREC.

Excipient warning

TYREC contains lactose. Patients with the rare hereditary conditions of galactose

intolerance total lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take TYREC.

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 as in TYREC 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 limited expression of CYP1A1 in human tissues.

When erlotinib as in TYREC 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 erlotinib. If adverse events related to erlotinib are observed, the dose of erlotinib may be reduced.

Pre-treatment or co-administration of erlotinib as in TYREC 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 %. It is documented that, 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. It is documented that, 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 as in TYREC should be reduced, particularly if toxicity is observed.

Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. It is documented that 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 in TYREC, 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 TYREC 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 erlotinib as in TYREC, 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 as in TYREC. Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

Erlotinib and coumarin-derived 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 erlotinib as in TYREC. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

Erlotinib and statins

The combination of erlotinib as in TYREC 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 as in TYREC in smokers as compared to non-smokers (see section 5.2).

Smokers should be advised to stop smoking for cigarette smoking, which is known to induce CYP1A1 and CYP1A2, has been shown to reduce erlotinib exposure by 50 – 60 % (see section 4.2, 4.4, 5.1 and 5.2).

Efficacy in smoking patients has not been established.

Erlotinib and P-glycoprotein inhibitors

Erlotinib as in TYREC is a substrate for the P-glycoprotein, (Pgp) 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.

Erlotinib and medicines altering pH

Erlotinib as in TYREC is characterised by a decrease in solubility at pH above 5. Medicines that alter the pH of the upper Gastro-Intestinal (GI) tract, like proton pump inhibitors, H2 antagonists and antacids, may alter the solubility of erlotinib as in TYREC and hence its bioavailability. 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.

The effect of antacids and H2 antagonists on the absorption of erlotinib as in TYREC, has not been investigated but absorption may be impaired, leading to lower plasma levels. 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. Increasing the dose of TYREC, when co-administered with such medicines is not likely to compensate for the loss of exposure, therefore, concomitant administration of these combinations should be avoided. If the use of antacids is

considered necessary during treatment with TYREC, they should be taken at least 4 hours before or 2 hours after the daily dose of TYREC.

If the use of ranitidine is considered, it should be used in a staggered manner, i.e. TYREC 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

No significant effects of gemcitabine on the pharmacokinetics of erlotinib as in TYREC, nor significant effects of erlotinib as in TYREC on the pharmacokinetics of gemcitabine, were documented.

Erlotinib and Carboplatin/Paclitaxel

Erlotinib increases platinum concentrations. It has been documented that the concomitant use of erlotinib as in TYREC, 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 as in TYREC.

Erlotinib and Capecitabine

Capecitabine may increase erlotinib as in TYREC 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 documented, in which erlotinib was given as single medicine. 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 erlotinib as in TYREC. Such influence is supported by documented data, 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 TYREC. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy.

Pregnancy

There are no adequate data for the use of erlotinib as in TYREC in pregnant women. Animal studies have shown no evidence of teratogenicity or abnormal parturition, however, an adverse effect on the pregnancy cannot be excluded as rat and rabbit studies have shown increased embryo/foetal lethality. The potential risk for humans is unknown. Women who are pregnant should not receive TYREC.

Breastfeeding

It is not known whether erlotinib as in TYREC is excreted in human milk. No studies have been conducted to assess the impact of erlotinib on milk production or its presence in breast milk. As the potential harm to the nursing infant is unknown, woman should be advised against breastfeeding while receiving TYREC 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; however, TYREC is not associated with impairment of mental ability.

4.8 Undesirable effects

a. Summary of the safety profile

Side effects/adverse events which have been observed and documented in patients with bronchial adenocarcinoma, who were treated with erlotinib as in TYREC, as monotherapy, were the following. 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 may be advisable. Skin fissures, mostly non-serious, were reported, most were associated with rash and dry skin.

Where erlotinib was administered as maintenance after first-line chemotherapy, or first-line treatment of bronchial adenocarcinoma patients with EGFR activating mutations, no new safety signals were identified. The most frequent side effects seen were rash and diarrhoea.

In pancreatic cancer patients receiving erlotinib plus gemcitabine, fatigue, rash and diarrhoea were the most frequent side effects.

b. Tabulated summary of adverse reactions

Possibly related undesirable effects that have been reported in patients who received erlotinib as in TYREC, as a single medicine, and in patients who received

erlotinib as in TYREC, concurrently with chemotherapy, are listed in the table below. All known ADRs are listed by system organ class and frequency: more frequent, frequent, less frequent or frequency unknown.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Infection, including pneumonia, sepsis, and cellulitis
Metabolism and nutrition disorders	Frequent	Anorexia, decreased weight
Psychiatric disorders	Frequent	Depression
Nervous system disorders	Frequent	Headache, neuropathy
Eye disorders	Frequent	Keratitis and conjunctivitis
	Less frequent	Eyelash changes, corneal perforations, corneal ulcerations, uveitis
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, epistaxis, cough
	Less frequent	Serious interstitial lung disease (ILD), including fatalities
Gastrointestinal disorders	Frequent	Diarrhoea, stomatitis, dyspepsia flatulence, nausea, vomiting, abdominal pain, gastrointestinal bleeding, including fatalities.
	Less frequent	Gastrointestinal perforations, including fatalities
Hepato-biliary disorders	Frequent	Liver function test abnormalities (including increased alanine aminotransferase [ALT],

MedDRA system organ class	Frequency	Adverse reactions
		aspartate aminotransferase [AST], bilirubin)
	Less frequent	Hepatic failure (including fatalities)
Skin and subcutaneous tissue disorders	Frequent	Alopecia, paronychia, dry skin, acne, dermatitis acneiform, folliculitis, rash
	Less frequent	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, palmar plantar erythrodys – aesthesia syndrome
General disorders and administration site conditions	Frequent	Pyrexia, fatigue, rigors

c. Description of selected adverse reactions

Corneal ulcerations and perforations have been reported less frequently in patients receiving TYREC as a complication of mucocutaneous inflammation.

Eyelash changes can include in-growing eyelashes, excessive growth and thickening of the eyelashes.

It has been documented that in some cases gastrointestinal bleeding, including fatalities, has been associated with concomitant warfarin administration (see section 4.5) and some with concomitant NSAID administration.

Diarrhoea can lead to dehydration, hypokalaemia, and renal failure.

e. Other special population(s)

Cases of hepatic failure (including fatalities) have been reported during use of TYREC. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications (see section 4.4).

Liver function test abnormalities (including increased alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin) were mainly mild or moderate in severity, transient in nature or associated with liver metastases.

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 **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

It is documented that single oral doses of erlotinib as in TYREC, up to 1 000 mg in healthy subjects, and up to 1 600 mg in cancer patients given once weekly 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 data documented, severe adverse events such as diarrhoea, rash and possibly liver transaminase elevation may occur above the recommended dose.

Management

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent protein kinase inhibitor.

ATC code: L01XE03.

Pharmacological classification: A 26 – Cytostatics

Mechanism of action

Erlotinib is an epidermal growth factor receptor (EGFR), also known as human epidermal growth factor receptor type 1 (HER1) tyrosine kinase inhibitor and inhibits the intracellular phosphorylation of EGFR/ 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 and distributes into tumour tissue of humans. It has been documented that after 4 subjects (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 averaged at 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 the liver of humans, by hepatic cytochrome P450 enzymes, primarily CYP3A4, and to a lesser extent by CYP1A2. 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 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 OSI-420 and OSI-413 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 in plasma 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 (> 90 %), with renal elimination accounting for only a small amount of an oral dose.

Documented data 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-medicine pharmacokinetic analysis. No new covariate effects were identified. Co-administration of gemcitabine had no effect on erlotinib plasma clearance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium lauryl sulfate

Sodium starch glycolate

Tablet coating

Hydroxypropyl cellulose (E463)

Hypromellose (E464)

Macrogol

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

TYREC 25: Clear PVC – Aluminium foil blister pack, containing 10 film-coated tablets, in an outer carton.

TYREC 100: Clear PVC – Aluminium foil blister pack, containing 10 film-coated tablets, in an outer carton.

TYREC 150: Clear PVC – Aluminium foil blister pack, containing 10 film-coated tablets, in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Kahma Biotech (Pty) Ltd

106, 16th Road

Midrand

8 REGISTRATION NUMBERS

TYREC 25 550660

TYREC 100 550661

TYREC 150 550662

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 January 2023

10 DATE OF REVISION OF THE TEXT