APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ERLOTINIB 25 mg ADCO film-coated tablets

ERLOTINIB 100 mg ADCO film-coated tablets

ERLOTINIB 150 mg ADCO film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

Excipients with known effect

Each 25 mg film-coated tablet contains 17,66 mg lactose monohydrate.

Each 100 mg film-coated tablet contains 70,65 mg lactose monohydrate.

Each 150 mg film-coated tablet contains 105,98 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

ERLOTINIB 25 mg ADCO: White, round biconvex tablet with “E9OB” debossed on one side and “25” on the other. The tablets have a diameter of approximately 6 mm.

ERLOTINIB 100 mg ADCO: White, round, biconvex tablets with a score line on both sides, on one side the tablet is debossed with “E9OB” above the score line and “100” below the score line. The tablets have a diameter of approximately 10 mm.

The tablet can be divided into equal halves, each containing 50 mg erlotinib.

ERLOTINIB 150 mg ADCO: White, round, biconvex tablets with “E9OB” debossed in one side and “150” in the other. The tablets have a diameter of approximately 10.4 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-Small Cell Lung Cancer (NSCLC):

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

ADCO ERLOTINIB 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

ADCO ERLOTINIB 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 ADCO ERLOTINIB, 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

Pancreatic Cancer

ADCO ERLOTINIB 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

ADCO ERLOTINIB 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 ADCO ERLOTINIB 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 ADCO ERLOTINIB 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 ADCO ERLOTINIB to patients with hepatic impairment. See section 5.2.

ADCO ERLOTINIB should not be used in patients with severe hepatic dysfunction (AST and ALT > 5 x ULN).

Dose reduction or interruption of ADCO ERLOTINIB 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 ADCO ERLOTINIB has not been studied in patients with renal impairment. See section 5.2.

ADCO ERLOTINIB 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 ADCO ERLOTINIB in NSCLC and bronchial adenocarcinoma patients who currently smoke cigarettes was 300 mg. The 300 mg dose did not show improved efficacy in second line treatment after failure of chemotherapy compared to the recommended 150 mg dose in patients who continue to smoke cigarettes.

Paediatric use

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

4.3 Contraindications

- Hypersensitivity to the erlotinib or to any of the excipients listed in section 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, as contained in ADCO 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 (0,8 %) was the same in both the placebo and erlotinib groups.

In the pancreatic cancer study in combination with gemcitabine, the incidence of ILD-like events was 2,5 % in the erlotinib, as contained in ADCO 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 therapy with erlotinib, as contained in ADCO ERLOTINIB.

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, ADCO ERLOTINIB therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, ADCO ERLOTINIB 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 as contained in ADCO ERLOTINIB and moderate or severe diarrhoea should be treated with e.g. loperamide. In some cases dose reduction may be necessary.

In the clinical studies doses were reduced by 50 mg steps. Dose reductions by 25 mg steps have not been investigated. In the event of severe or persistent diarrhoea, nausea, anorexia, or vomiting associated with dehydration, ADCO ERLOTINIB 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 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 groups of patients with aggravating risk factors (especially concomitant chemotherapy and other medications, symptoms or diseases or other predisposing conditions including advanced age), ADCO ERLOTINIB 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, as contained in ADCO ERLOTINIB. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications. Therefore, in such patients, periodic liver function testing should be considered. ADCO ERLOTINIB dosing should be interrupted if changes in liver function are severe (see section 4.8). ADCO ERLOTINIB is not recommended for use in patients with severe hepatic dysfunction.

Gastrointestinal perforation

Patients receiving ADCO ERLOTINIB are at 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. ADCO ERLOTINIB should be permanently discontinued in patients who develop gastrointestinal perforation (see section 4.8).

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). ADCO ERLOTINIB treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

Patients with bullous and exfoliative skin disorders should be tested for skin infection and treated according to local management guidelines.

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

Ocular disorders

Cases of corneal perforation or ulceration, uveitis, iridocyclitis and iritis have been reported during use of ADCO ERLOTINIB. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with ADCO ERLOTINIB treatment which are also risk factors for corneal perforation/ulceration. ADCO ERLOTINIB therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain.

Smokers

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

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

Ischaemic Central Nervous System Vascular Condition Associated with Tyrosine Kinase Inhibitors (TKI)

Cerebrovascular adverse events may occur in patients on treatment with TKI containing medicines with or without risk factors for these events and may occur at any time during treatment with TKIs (see section 4.8). Patients on treatment with TKI containing medicine should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events.

Treatment with TKI containing medicines should be discontinued, and alternative treatment options be

considered in patients who develop these class related cerebrovascular adverse events.

Assessment of EGFR mutation status

When considering the use of ADCO ERLOTINIB 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 tumor 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:

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 agents 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 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 ADCO ERLOTINIB when co-administered with such agents 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. Concomitant administration of these combinations should therefore be avoided (see section 4.5). If the use of antacids is considered necessary during treatment with ADCO ERLOTINIB, they should be taken at least 4 hours before or 2 hours after the dailiy dose of ADCO ERLOTINIB.

ADCO ERLOTINIB contains lactose.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-glactose malabsorption should not take ADCO ERLOTINIB.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

ADCO ERLOTINIB and other CYP substrates

Erlotinib, as contained in ADCO 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 tissue.

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

Pretreatment or co-administration of ADCO 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 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 contained in ADCO ERLOTINIB 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 ADCO ERLOTINIB, as compared to ADCO ERLOTINIB alone.

Pre-treatment and co-administration of rifampicin with a single 450 mg dose of ADCO ERLOTINIB resulted in a mean erlotinib exposure (AUC) of 57,5 % of that after a single 150 mg ADCO ERLOTINIB dose in the absence of rifampicin treatment. Co-administration of ADCO ERLOTINIB 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 ADCO ERLOTINIB 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. Johns 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.

Interactions with warfarin

Interaction 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 contained in ADCO ERLOTINIB. Patients taking warfarin should be monitored regularly for any changes in prothrombin time or INR.

ADCO ERLOTINIB and statins

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

ADCO 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 ADCO 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, 5.1 and 5.2).

ADCO ERLOTINIB and P-glycoprotein inhibitors

Erlotinib, as contained in ADCO 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 ADCO ERLOTINIB.

The consequences of this interaction for e.g. CNS toxicity have not been established. Caution should be exercised in such situations.

ADCO 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 [Cmax] by 46 % and 61 %, respectively.

There was no change to Tmax or half-life. Therefore, medicines that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its bioavailability.

Increasing the dose of ADCO ERLOTINIB 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 ADCO 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. If the use of antacids is considered necessary during treatment with ADCO ERLOTINIB, they should be taken at least 4 hours before or 2 hours after the daily dose of ADCO ERLOTINIB.

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

ADCO 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.

ADCO 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.

ADCO ERLOTINIB and capecitabine

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

ADCO ERLOTINIBand 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 of childbearing potential

Women of childbearing potential must be advised to avoid pregnancy while on ADCO ERLOTINIB. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the foetus.

Pregnancy

There are no adequate data for the use of ADCO ERLOTINIB in pregnant women. Studies in animals have

shown no evidence of teratogenicity or abnormal parturition. However, studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Breastfeeding

It is not known whether erlotinib is excreted in human milk. No data is available regarding the impact of ADCO ERLOTINIB on milk production. Because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving ADCO ERLOTINIB 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 erlotinib is not associated with impairment of mental ability.

Ocular disorders have been observed with ADCO ERLOTINIB treatment, affecting a a person's ability to safely drive and use macines (see section 4.4, 4.8).

4.8 Undesirable effects

Summary of the safety profile

ADCO ERLOTINIB monotherapy

The most frequently reported side effects were rash and diarrhoea.

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 sun screen (e.g. mineral-containing) may be advisable. Skin fissures, mostly non-serious, were reported, most

were associated with rash and dry skin.

Table 1: Tabulated summary of adverse effects:

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Infections and infestations	Frequent	Infection
Metabolism and nutrition disorders	Frequent	Anorexia Decrease in weight
Psychiatric disorders	Frequent	Depression
Nervous system disorders	Frequent	Neuropathy
Eye disorders	Frequent	Cojunctivitis Keratoconjunctivitis sicca Keratitis
	Less frequent	Eyelash changes (including in-growing eyelashes, excessive growth and thickening of the eyelashes) Corneal perforations Corneal ulcerations Uveitis
Vascular disorders	Frequent	Cerebrovascular Accident
	Less frequent	Transient Ischaemic Attack Cerebral Infarction Ischaemic stroke
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea Cough Epistaxis
	Less frequent	Interstitial lung disease (ILD) (including

		fatalities in patients with NSCLC and other advanced solid tumours)
Gastrointestinal disorders	Frequent	Diarrhoea (including fatalities) Nausea Vomiting Stomatitis Abdominal pain Dyspepsia Flatulence Gastrointestinal bleeding (including fatalities)
	Less frequent	Gastrointestinal perforations (including fatalities)
Hepato biliary disorders	Frequent	Liver function test abnormalities (including increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin)
	Less frequent	Hepatic failure (including fatalities)
Skin and subcutaneous tissue disorders	Frequent	Rash (mild to moderate) Pruritis Dry skin Alopecia Paronychia Folliculitis (mild to moderate and non-serious) Acne/Dermatitis acneiform Skin fissures

	Less frequent	Hirsutism Eyebrow changes Brittle and loose nails Hyperpigmentation Palmar plantar erythrodysaesthesia syndrome Stevens-Johnson syndrome / Toxic epidermal necrolysis (including fatalities)
Renal and urinary disorders	Frequent	Renal insufficiency
	Less frequent	Nephritis
		Proteinuria
General disorders and administration site conditions	Frequent	Fatigue Pyrexia Rigors

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 asked to report any suspected adverse reactions to SAHPRA via the eReporting link at https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=ZA

4.9 Overdose

Symptoms

Single oral doses of ADCO ERLOTINIB up to 1000 mg in healthy subjects, and up to 1600 mg 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 reactions such as diarrhoea, rash and possibly increased liver transaminases may occur above the recommended dose.

Management

In case of suspected overdose, ADCO ERLOTINIB 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

Elotinib absorbed after oral administration 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 of 1,995 ng/ml is achieved. 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 is 41,300 μg*hr/ml.

Distribution

Erlotinib has a mean apparent volume of distribution of 232 L and 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 averaged 1185 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 tumour 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 the lungs, and CYP1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib. *In vitro* studies indicate approximately 80 – 95 % of erlotinib is metabolised by the CYP3A4 enzyme.

The three main metabolic pathways identified are:

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 < 10 % of erlotinib and display similar pharmacokinetics as erlotinib.

Elimination

Trace amounts of erlotinib and its metabolites 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 medicine erlotinib shows 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.

Pharmacokinetics in special populations

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 $AUC_{0-infinity}$ in smokers was about 1/3 of that in non-smokers. 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).

Elderly population

There have been no specific studies in elderly patients.

Hepatic impairment

Erlotinib is primarily 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.

Paediatric poplation

There have been no specific studies in paediatric patients

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate

Cellulose microcrystalline

Calcium hydrogen phosphate anhydrous

Sodium starch glycolate

Silica colloidal anhydrous

Sodium laurilsulfate

Magnesium stearate

Tablet coat

Hypromellose

Hydroxypropylcellulose

Titanium dioxide

Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This product does not require any special storage conditions.

6.5 Nature and contents of container

OPA/Alu/PVC and Alu (Alu/Alu) blister strips, packed into a carton.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road,

Erand Gardens,

Midrand, 1685

www.adcock.com

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

ERLOTINIB 25 mg ADCO: 54/26/0808

ERLOTINIB 100 mg ADCO: 54/26/0809

ERLOTINIB 150 mg ADCO: 54/26/0810

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 August 2022

10. DATE OF REVISION OF THE TEXT