For the Use of a Registered Medical Practitioner only

PRESCRIBING INFORMATION

TARLONIB 25, 100 and 150
(Erlotinib tablets 25 mg, 100 mg and 150 mg)

COMPOSITION

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

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

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

Excipients*:* Lactose Monohydrate, Microcrystalline cellulose, Sodium starch glycolate, Sodium lauryl sulphate, Magnesium stearate, Microcrystalline cellulose, Opadry.

PRODUCT DESCRIPTION

TARLONIB 25 are are white to off white round biconvex film coated tablets debossed with "RL" on one side and "11" on other side.

TARLONIB 100 are White to off white round biconvex film coated tablets debossed with "RL" on one side and "12" on other side.

TARLONIB 150 are White to off white round biconvex film coated tablets debossed with "RL" on one side and "13" on other side.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

- Pharmacodynamics

Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor. Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR is expressed on the cell surface of normal cells and cancer cells. It is reported that the inhibition of EGFR phosphotyrosine results in cell stasis and/or death.

EGFR mutations may lead to constitutive activation of anti-apoptotic and proliferation signaling pathways. The potent effectiveness of erlotinib in blocking EGFR-mediated signalling in these EGFR mutation positive tumours is attributed to the tight binding of erlotinib to the ATP-binding site in the mutated kinase domain of the EGFR. Due to the blocking of downstream-signaling, the proliferation of cells is stopped, and cell death is induced through the intrinsic apoptotic pathway. Tumour regression has been reported in mouse models of enforced expression of these EGFR activating mutations.

- Pharmacokinetics

Absorption

After oral administration, erlotinib peak plasma levels are obtained in approximately 4 hours after oral dosing. Absolute bioavailability of erlotinib is 59% in normal healthy volunteers. The exposure after an oral dose may be increased by food.

Distribution

Erlotinib has a mean apparent volume of distribution of 232 l and distributes into tumour tissue of humans. Tumour concentrations of erlotinib was reported as 1185 ng/g of tissue (average value) in patients with non-small cell lung cancer [NSCLC] and patient with laryngeal cancer who received oral doses of erlotinib 150 mg daily for 9 days. This corresponded to an overall average of 63% (range 5-161%) of the steady state reported 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% (range 88-130%) of the reported 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 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 1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib.

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. They are present in plasma at levels that are <10% of erlotinib and display similar pharmacokinetics as erlotinib.

Elimination:
Erlotinib is excreted predominantly as metabolites *via* the faeces (>90%) with renal elimination accounting for only a small amount (approximately 9%) of an oral dose. Less than 2% of the orally administered dose is excreted as parent substance. A mean apparent clearance of 4.47 l/hour with a median half-life of 36.2 hours has been reported in patients receiving single agent erlotinib. Therefore, the time to reach steady state plasma concentration would be expected to occur in approximately 7-8 days.

Pharmacokinetics in special populations:
No clinically significant relationship between predicted apparent clearance and patient age, bodyweight, gender and ethnicity has been reported. 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. However, smokers had an increased rate of erlotinib clearance. This was confirmed in non-smoking and currently cigarette smoking healthy subjects receiving a single oral dose of 150 mg erlotinib. The geometric mean of the C_{max} was 1056 ng/mL in the non-smokers and 689 ng/mL in the smokers with a mean ratio for smokers to non- smokers of 65.2% (95% CI: 44.3 to 95.9, p = 0.031). The geometric mean of the AUC_{0-inf} was 18726 ng•h/mL in the non-smokers and 6718 ng•h/mL in the smokers with a mean ratio of 35.9% (95% CI: 23.7 to 54.3, p < 0.0001). The geometric mean of the C_{24h} was 288 ng/mL in the non-smokers and 34.8 ng/mL in the smokers with a mean ratio of 12.1% (95% CI: 4.82 to 30.2, p = 0.0001).

In patients with NSCLC, current smokers achieved erlotinib steady state trough plasma concentration of 0.65 µg/mL which was approximately 2-fold less than the former smokers or patients who had never smoked (1.28 µg/mL). This effect was accompanied by a 24% increase in apparent erlotinib plasma clearance. 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 was reported as 1.22 µg/mL.

Based on the above, current smokers should be advised to stop smoking while taking erlotinib, as plasma concentrations could be reduced otherwise.

It has been reported that the presence of an opioid appeared to increase exposure by about 11%.

It is reported that covariants affecting erlotinib clearance in pancreatic cancer patients who received erlotinib plus gemcitabine were very similar to those reported in the prior single agent pharmacokinetic analysis. No new covariate effects were identified. Co- administration of gemcitabine had no effect on erlotinib plasma clearance.

Paediatric population: There have been no specific studies in paediatric patients.

Elderly population: There have been no specific studies in elderly patients.

Hepatic impairment: Erlotinib is primarily cleared by the liver. In patients with solid tumours and with moderately impaired hepatic function (Child-Pugh score 7-9), geometric mean erlotinib AUC_{0-t} and C_{max} was 27000 ng•h/mL and 805 ng/mL, respectively, as compared to 29300 ng•h/mL and 1090 ng/mL in patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases. Although the C_{max} was statistically significant lower in moderately hepatic impaired patients, this difference is not considered clinically relevant. No information is available regarding the influence of severe hepatic dysfunction on the pharmacokinetics of erlotinib. It has been reported that increased serum concentrations of total bilirubin were associated with a slower rate of erlotinib clearance.

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 clinically significant relationship has been reported between erlotinib clearance and creatinine clearance, but there are no information is available for patients with creatinine clearance <15 ml/min.

INDICATIONS

Non-Small Cell Lung Cancer (NSCLC):

TARLONIB is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations. TARLONIB is indicated for maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations who have not progressed after first-line chemotherapy.

TARLONIB is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

Pancreatic Cancer

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

DOSE AND METHOD OF ADMINISTRATION

Standard Dosage

Non-small cell lung cancer
EGFR mutation testing should be performed prior to initiation of TARLONIB as first-line or maintenance therapy in patients with locally advanced or metastatic NSCLC.

The recommended daily dose of TARLONIB is 150 mg taken at least one hour before or two hours after the ingestion of food.

Pancreatic Cancer
The recommended daily dose of TARLONIB is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the package insert of gemcitabine for the pancreatic cancer indication)

Special Dosage Instructions

Drug Interactions: Concomitant use of CYP 3A4 substrates and modulators may require dose adjustment (see DRUG INTERACTIONS).

When dose adjustment is necessary, it is RECOMMENDED TO REDUCE IN 50 MG STEPS (SEE WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

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 TARLONIB to patients with hepatic impairment. Dose reduction or interruption of TARLONIB should be considered if severe adverse reactions occur. Safety and efficacy have not been studied in patients with severe hepatic impairment (see WARNINGS AND PRECAUTIONS] and Pharmacokinetics in Special Populations)

Renal impairment: The safety and efficacy of TARLONIB has not been studied in patients with renal impairment. (see Pharmacokinetics in Special Populations).

Pediatric use: The safety and efficacy of TARLONIB in the approved indications has not been established in patients under the age of 18 years.

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

cigarettes (see DRUG INTERACTIONS and Pharmacokinetics in Special Populations).

CONTRAINDICATIONS

Hypersensitivity to erlotinib or to any of the excipients of this product.

WARNINGS AND PRECAUTIONS

Assessment of EGFR mutation status

When assessing the EGFR mutation status of a patient, it is important that a well- validated and robust methodology is chosen to avoid false negative or false positive determinations.

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 DRUG INTERACTIONS).

Interstitial Lung Disease

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

In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, erlotinib 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, erlotinib should be discontinued and appropriate treatment initiated as necessary (see SIDE EFFECTS/UNDESIRABLE EFFECTS).

Diarrhoea, dehydration, electrolyte imbalance and renal failure

Diarrhoea (including very rare cases with a fatal outcome) has occurred in approximately 50% of patients on erlotinib and moderate or severe diarrhoea should be treated with e.g. loperamide. In some cases dose reduction may be necessary. In the event of severe or persistent diarrhoea, nausea, anorexia, or vomiting associated with dehydration, erlotinib therapy should be interrupted and appropriate measures should be taken to treat the dehydration (see SIDE EFFECTS/UNDESIRABLE EFFECTS). There have been rare 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), 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

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

Gastrointestinal perforation

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

Bullous and exfoliative skin disorders

Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal (see SIDE EFFECTS/UNDESIRABLE EFFECTS). 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.

Ocular disorders

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with erlotinib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Erlotinib 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. Very rare cases of corneal perforation or ulceration have been reported during use of erlotinib (see SIDE EFFECTS/UNDESIRABLE EFFECTS).

Interactions with other medicinal products

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 agents should be avoided (see DRUG INTERACTIONS).

Other forms of interactions

Erlotinib is characterised by a decrease in solubility at pH above 5. Medicinal products 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 and hence its bioavailability. Increasing the dose of 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. Therefore, concomitant administration of these combinations should be avoided (see DRUG INTERACTIONS). If the use of antacids is considered necessary during treatment with erlotinib, they should be taken at least 4 hours before or 2 hours after the daily dose of erlotinib.

TARLONIB contain lactose and should not be administered to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose- galactose malabsorption.

DRUG INTERACTIONS

Erlotinib and other CYP substrates

Erlotinib is a potent inhibitor of CYP1A1, and a moderate inhibitor of CYP3A4 and CYP2C8, as well as a strong inhibitor of glucuronidation by UGT1A1 *in vitro*.

The physiological relevance of the strong inhibition of CYP1A1 is unknown due to the very limited expression of CYP1A1 in human tissues.

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

Pre-treatment or co-administration of erlotinib did not alter the clearance of the prototypical CYP3A4 substrates, midazolam and erythromycin, but did appear to decrease the oral bioavailability of midazolam by up to 24%. Erlotinib was reported 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 medicinal products 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. Therefore, caution should be used when erlotinib is combined with a potent CYP3A4 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 metabolism and significantly decrease erlotinib plasma concentrations. Co-administration of erlotinib with CYP3A4i inducers should therefore be avoided. For patients who require concomitant treatment with 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. 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.

Erlotinib and coumarin-derived anticoagulants

Interaction with coumarin-derived anticoagulants including warfarin leading to increased International Normalized Ratio (INR) and bleeding events, which in some cases were fatal, have been reported in patients receiving erlotinib. Patients taking coumarin-derived anticoagulants should be monitored regularly for any changes in prothrombin time or INR.

Erlotinib and statins

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

Erlotinib and smokers

A significant reduction in AUC_{inf}, C_{max} and plasma concentration at 24 hours has been reported after administration of erlotinib in smokers as compared to non-smokers. Therefore, patients who are still smoking should be encouraged to stop smoking as early as possible before initiation of treatment with erlotinib, as plasma erlotinib concentrations are reduced otherwise. The clinical

effect of the decreased exposure has not been formally assessed but it is likely to be clinically significant.

Erlotinib and P-glycoprotein inhibitors

Erlotinib is a substrate for the P-glycoprotein active substance transporter. Concomitant administration of inhibitors of Pgp, e.g. cyclosporine 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 medicinal products altering pH

Erlotinib is characterised by a decrease in solubility at pH above 5. Medicinal products that alter the pH of the upper Gastro-Intestinal (GI) tract may alter the solubility of erlotinib 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. Concomitant administration of erlotinib with 300 mg ranitidine, an H_2-receptor antagonist, decreased erlotinib exposure [AUC] and maximum concentrations [C_{max}] by 33% and 54%, respectively. Increasing the dose of erlotinib when co-administered with such agents is not likely to compensate for this loss of exposure. However, when erlotinib was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg b.i.d., erlotinib exposure [AUC] and maximum concentrations [C_{max}] decreased only by 15% and 17%, respectively. The effect of antacids on the absorption of erlotinib has not been investigated but absorption may be impaired, leading to lower plasma levels. In summary, the combination of erlotinib with proton pump inhibitors should be avoided. If the use of antacids is considered necessary during treatment with erlotinib, they should be taken at least 4 hours before or 2 hours after the daily dose of erlotinib. 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 ranitidine dosing.

Erlotinib and Gemcitabine

It has been reported that there were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine.

Erlotinib and Carboplatin/Paclitaxel

Erlotinib increases platinum concentrations. It has been reported that the concomitant use of erlotinib with carboplatin and paclitaxel led to an increase of total platinum AUC_{0-48} of10.6%. Although statistically significant, the magnitude of this difference is not considered to be clinically relevant. In clinical practice, there may be other co-factors leading to an increased exposure to carboplatin like renal impairment. There were no significant effects of carboplatin or paclitaxel on the pharmacokinetics of erlotinib.

Erlotinib and Capecitabine

Capecitabine may increase erlotinib 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 in which erlotinib was given as single agent. There were no significant effects of erlotinib on the pharmacokinetics of capecitabine.

Erlotinib and Proteasome Inhibitors

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

USE IN SPECIAL POPULATIONS

Pregnancy

There are no adequate information reported for the use of erlotinib in pregnant women. No evidence of teratogenicity or abnormal parturition have been reported in animal studies. However, an adverse effect on the pregnancy cannot be excluded as rat and rabbit studies have reported an increased embryo/foetal lethality, the potential risk for humans is unknown.

Women of childbearing potential

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

Fertility

No evidence of impaired fertility have been reported in animal studies. However, an adverse effect on the fertility cannot be excluded as animal studies have been reported for effects on reproductive parameters .The potential risk for humans is unknown.

Lactation

It is not known whether erlotinib is excreted in human milk. Because of the potential harm to the infant, mothers should be advised against breast-feeding while receiving erlotinib.

SIDE EFFECTS/UNDESIRABLE EFFECTS

Non-small cell lung cancer (erlotinib administered as monotherapy):

Rash and diarrhoea were the most commonly reported adverse drug reactions (ADRs). Most were Grade 1/2 in severity and manageable without intervention. Grade 3/4 rash and diarrhoea reported in erlotinib-treated patients and each resulted in treatment discontinuation. The median time to onset of rash was 8 days, and the median time to onset of diarrhoea was 12 days.

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.

Adverse reactions occurring more frequently in erlotinib-treated patients than in the patients who received placebo are summarised in Table 1.

Table 1: Very common ADRs NCI-CTC Grade
MedDRA Preferred Term
Infections and infestations Infection*
Metabolism and nutrition disorders Anorexia
Eye disorders Keratoconjunctivitis sicca Conjunctivitis
Respiratory, thoracic and mediastinal disorders Dyspnoea, Cough
Gastrointestinal disorders Diarrhoea**, Nausea, Vomiting, Stomatitis, Abdominal pain
Skin and subcutaneous tissue disorders Rash***, Pruritus, Dry skin
General disorders and administration site conditions Fatigue

* Severe infections, with or without neutropenia, have included pneumonia, sepsis, and cellulitis.
** Can lead to dehydration, hypokalemia and renal failure.
*** Rash included dermatitis acneiform.

Pancreatic cancer (erlotinib administered concurrently with gemcitabine):
The most common adverse reactions in pancreatic cancer patients who received erlotinib 100 mg plus gemcitabine were fatigue, rash and diarrhoea. Adverse reactions reported more frequently in erlotinib 100 mg plus gemcitabine- treated patients than in patients who received placebo plus gemcitabine are summarised in Table 2.

Table 2: Very common ADRs

NCI-CTC Grade
MedDRA Preferred Term
Infections and infestations Infection*

Metabolism and nutrition disorders Weight decreased
Psychiatric disorders
Depression
Nervous system disorders Neuropathy, Headache
Respiratory ,thoracic and mediastinal disorders Cough
Gastrointestinal disorders Diarrhoea** Stomatitis Dyspepsia Flatulence
Skin and subcutaneous tissue disorders Rash*** Alopecia
General disorders and administration site conditions Fatigue, Pyrexia, Rigors

* Severe infections, with or without neutropenia, have included pneumonia, sepsis, and cellulitis.

** Can lead to dehydration, hypokalemia and renal failure.

*** Rash included dermatitis acneiform.

Other Observations:

Safety evaluation of erlotinib is based on the data from patients treated with at least one 150 mg dose of erlotinib monotherapy and patients who received erlotinib 25, 100 or 150 mg in combination with gemcitabine.

The following adverse reactions have been reported in patients who received erlotinib administered as single agent and patients who received erlotinib concurrently with chemotherapy.

Very common ADRs are presented in Tables 1 and 2, other ADRs are summarized in Table 3.

Table 3: Summary of ADRs per frequency category

Body System	Very common	Common	Uncommon	Rare	Very rare
Eye disorders		-Keratitis - Conjunctivitis	-Eyelash changes		-Corneal perforations -Corneal ulcerations -Uveitis
Respiratory, thoracic and mediastinal disorders		-Epistaxis	-Interstitial lung disease (ILD)		

Gastro-intestinal disorders	-Diarrhoea	-Gastro-intestinal bleeding	-Gastro-intestinal perforations		
Hepato biliary disorders	-Liver function test abnormalities			-Hepatic failure	
Skin and subcutaneous tissue disorders		-Alopecia -Dry skin[1] -Paronychia -Folliculitis -Acne/ Dermatitis acneiform -Skin fissures	-Hirsutism -Eyebrow changes -Brittle and Loose nails -Mild skin reactions such as hyperpigmentation	-Palmar plantar erythrodys-aesthesia syndrome	-Stevens-Johnson syndrome/Toxic epidermal necrolysis
Renal and urinary disorders		-Renal insufficiency	-Nephritis -Proteinuria		

[1]In pancreatic cancer patients who received erlotinib 100 mg plus gemcitabine.

[2]Including in-growing eyelashes, excessive growth and thickening of the eyelashes.

[3]Including fatalities, in patients receiving erlotinib for treatment of NSCLC or other advanced solid tumours (see WARNINGS AND PRECAUTIONS). A higher incidence have been reported in patients in Japan.

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

[5]Including increased alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin. These were very common in pancreatic cancer patients who received erlotinib 100 mg plus gemcitabine and common in Non-small cell lung cancer patients who received erlotinib as second line therapy. Cases were mainly mild to moderate in severity, transient in nature or associated with liver metastases.

[6]Including fatalities. Confounding factors included pre-existing liver disease or concomitant hepatotoxic medications (see WARNINGS AND PRECAUTIONS).

[7]Including fatalities (see WARNINGS AND PRECAUTIONS).

OVERDOSE

Symptoms

Single oral doses of erlotinib up to 1000 mg erlotinib 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. Severe adverse reactions such as diarrhoea, rash and possibly increased activity of liver aminotransferases may occur above the recommended dose.

Management

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

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.

STORAGE

Store below 30°C.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN

SUPPLY

Desiccant embedded cold form blister pack of 3x10's per box.

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Manufactured In India by:
Sun Phannaceutical Industries Limited (SPIL),
Halo!-Baroda Highway,
Halol-389 350, Gujarat, India

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