PATIENT INFORMATION LEAFLET

ERLOZ 150 (Erlotinib Hydrochloride Tablets 150mg)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist, or nurse
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

1. What Erlotinib Hydrochloride Tablets is and what it is used for

Non-Small Cell Lung Cancer (NSCLC)

Erlotinib Tablets is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations.

Erlotinib Tablets is also indicated for switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease after first-line chemotherapy.

Erlotinib Tablets is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. In patients with tumours without EGFR activating mutations, Erlotinib Tablets is indicated when other treatment options are not considered suitable.

When prescribing Erlotinib Tablets, 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 Epidermal Growth Factor Receptor (EGFR)-IHC negative tumours.

Pancreatic cancer

Erlotinib Tablets in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer.

When prescribing Erlotinib Tablets, factors associated with prolonged survival should be taken into account.

No survival advantage could be shown for patients with locally advanced disease

2. What you need to know before you take Erlotinib Hydrochloride Tablets

Hypersensitivity to Erlotinib Tablets or to any of the excipients

Assessment of EGFR mutation status

When considering the use of Erlotinib Tablets 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 pre specified 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.

Smokers

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

Interstitial Lung Disease

Cases of interstitial lung disease (ILD)-like events, including fatalities, have been reported uncommonly in patients receiving Erlotinib Tablets 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 (0.8%) was the

same in both the placebo and Erlotinib Tablets groups. In a meta-analysis of NSCLC randomised controlled clinical trials (excluding phase I and single-arm phase II studies due to lack of control groups), the incidence of ILD-like events was 0.9% on Erlotinib Tablets compared to 0.4% in patients in the control arms. In the pancreatic cancer study in combination with gemcitabine, the incidence of ILD-like events was 2.5% in the

Erlotinib Tablets plus gemcitabine group versus 0.4% in the placebo plus gemcitabine treated group. 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. Symptoms started from a few days to several months after initiating Erlotinib Tablets therapy. Confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections were frequent. A higher incidence of ILD (approximately 5% with a mortality rate of 1.5%) is seen among patients in studies conducted in Japan.

In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, Erlotinib Tablets therapy should be interrupted pending diagnostic evaluation. Patients treated concurrently with erlotinib Tablets and gemcitabine should be monitored carefully for the possibility to develop ILD-like toxicity. If ILD is diagnosed, Erlotinib Tablets should be discontinued and appropriate treatment initiated as necessary .

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 Tablets 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, Erlotinib Tablets therapy should be interrupted and appropriate measures should be taken to treat the dehydration. 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 Tablets 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.

Hepatotoxicity

Serious cases of drug induced liver injury (DILI) including hepatitis, acute hepatitis and hepatic failure (including fatalities) have been reported during use of Erlotinib Tablets. Risk factors may include pre-existing liver disease or concomitant hepatotoxic medications. Periodic liver function testing is recommended during treatment with Erlotinib Tablets. The frequency of monitoring of liver function should be increased in patients with pre-existing hepatic impairment or biliary obstruction. Prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury. Erlotinib Tablets dosing should be interrupted if changes in liver function are severe . Erlotinib Tablets is not recommended for use in patients with severe hepatic dysfunction.

Gastrointestinal perforation

Patients receiving Erlotinib Tablets are at increased risk of developing gastrointestinal perforation, which was observed uncommonly (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 Tablets 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 very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal. Erlotinib Tablets 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 Tablets should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Erlotinib Tablets 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 Tablets.

Potent inducers of CYP3A4 may reduce the efficacy of Erlotinib Tablets whereas potent inhibitors of CYP3A4 may lead to increased toxicity. Concomitant treatment with these types of agents should be avoided.

Other forms of interactions

Erlotinib Tablets 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 Tablets and hence its bioavailability. Increasing the dose of Erlotinib Tablets when co-administered with such agents is not likely to compensate for the loss of exposure. Combination of Erlotinib Tablets with proton pump inhibitors should be avoided. The effects of concomitant administration of Erlotinib Tablets 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 Erlotinib Tablets, they should be taken at least 4 hours before or 2 hours after the daily dose of Erlotinib Tablets.

Excipients with known effect

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

This medicine contains less than 1 mmol sodium (less than 23 mg) per tablet, that is to say Erlotinib Tablets is essentially 'sodium -free'.

3. How to take Erlotinib Hydrochloride Tablets

Posology and method of administration

Erlotinib Tablets treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

Patients with Non-Small Cell Lung Cancer

EGFR mutation testing should be performed in accordance with the approved indications.

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

Patients with pancreatic cancer

The recommended daily dose of Erlotinib Tablets is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine. In patients who do not develop rash within the first 4 – 8 weeks of treatment, further Erlotinib Tablets treatment should be re-assessed

When dose adjustment is necessary, the dose should be reduced in 50 mg steps

Erlotinib Tablets is available in strengths of 25 mg, 100 mg and 150 mg.

Concomitant use of CYP3A4 substrates and modulators may require dose adjustment.

Hepatic impairment

Erlotinib is eliminated by hepatic metabolism and biliary excretion. Although Erlotinib Tablets 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 Erlotinib Tablets to patients with hepatic impairment. Dose reduction or interruption of Erlotinib Tablets should be considered if severe adverse reactions occur. The safety and efficacy of Erlotinib Tablets has not been studied in patients with severe hepatic dysfunction (AST/SGOT and ALT/SGPT> 5 x ULN). Use of Erlotinib Tablets in patients with Severe hepatic dysfunction is not recommended.

Renal impairment

The safety and efficacy of Erlotinib Tablets has not been studied in patients with renal impairment (serum creatinine concentration >1.5 times the upper normal limit). Based on pharmacokinetic data no dose adjustments appear necessary in patients with mild or moderate renal impairment. Use of Erlotinib Tablets in patients with severe renal impairment is not recommended.

Paediatric population

The safety and efficacy of erlotinib Tablets in the approved indications has not been established in patients under the age of 18 years. Use of Erlotinib in paediatric patients is not recommended.

Smokers

Cigarette smoking has been shown to reduce Erlotinib Tablets exposure by 50-60%. The maximum tolerated dose of Erlotinib Tablets in NSCLC 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. Safety data were comparable between the 300 mg and 150 mg doses; however, there was a numerical increase in the incidence of rash, interstitial lung disease and diarrhoea, in patients receiving the higher dose of erlotinib. Current smokers should be advised to stop smoking.

4. Possible side effects

Safety evaluation of Erlotinib Tablets is based on the data from more than 1500 patients treated with at least one 150 mg dose of Erlotinib Tablets monotherapy and more than 300 patients who received Erlotinib Tablets 100 or 150 mg in combination with gemcitabine.

The incidence of adverse drug reactions (ADRs) from clinical trials reported with Erlotinib Tablets alone or in combination with chemotherapy are summarised by National Cancer Institute-

Common Toxicity Criteria (NCI-CTC) Grade in Table 1. The listed ADRs were those reported in at least 10% (in the Erlotinib Tablets group) of patients and occurred more frequently (≥3%) in patients treated with Erlotinib Tablets than in the comparator arm. Other ADRs including those from other studies are summarized in Table 2.

Adverse drug reactions from clinical trials (Table 1) and other ADRs (Table 2) are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Non-small cell lung cancer (Erlotinib Tablets administered as monotherapy)

First-Line Treatment of Patients with EGFR Mutations

In an open-label, randomised phase III study, ML20650 conducted in 154 patients, the safety of Erlotinib Tablets for first-line treatment of NSCLC patients with EGFR activating mutations was assessed in 75 patients; no new safety signals were observed in these patients.

The most frequent ADRs seen in patients treated with Erlotinib Tablets in study ML20650 were rash and diarrhoea (any Grade 80% and 57%, respectively), most were Grade 1/2 in severity and manageable without intervention. Grade 3 rash and diarrhoea occurred in 9% and 4% of patients, respectively. No Grade 4 rash or diarrhoea was observed. Both rash and diarrhoea resulted in discontinuation of Erlotinib Tablets in 1% of patients. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in 11% and 7% of patients, respectively.

Maintenance treatment

In two other double-blind, randomised, placebo-controlled Phase III studies BO18192 (SATURN) and BO25460 (IUNO); Erlotinib Tablets was administered as maintenance after first-line chemotherapy. These studies were conducted in a total of 1532 patients with advanced, recurrent or metastatic NSCLC following first-line standard platinum-based chemotherapy, no new safety signals were identified.

The most frequent ADRs seen in patients treated with Erlotinib Tablets in studies BO18192 and BO25460 were rash (BO18192: all grades 49.2%, grade 3: 6.0%; BO25460: all grades 39.4%, grade 3: 5.0%) and diarrhoea (BO18192: all grades 20.3%, grade 3: 1.8%; BO25460: all grades 24.2%, grade 3: 2.5%). No Grade 4 rash or diarrhoea was observed in either study. Rash and diarrhoea resulted in discontinuation of Erlotinib Tablets in 1% and <1% of patients, respectively, in study BO18192, while no patients discontinued for rash or diarrhoea in BO25460. Dose modifications (interruptions or reductions) for rash and diarrhea were needed in 8.3% and 3% of

patients, respectively, in study BO18192 and 5.6% and 2.8% of patients, respectively, in study BO25460.

Second and Further Line Treatment

In a randomised double-blind study (BR.21; Erlotinib Tablets administered as second line therapy), rash (75%) and diarrhoea (54%) 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 occurred in 9% and 6%, respectively in Erlotinib Tablets-treated patients and each resulted in study discontinuation in 1% of patients. Dose reduction for rash and diarrhoea was needed in 6% and 1% of patients, respectively. In study BR.21, 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 sunscreen (e.g. mineral-containing) may be advisable.

Pancreatic cancer (Erlotinib Tablets administered concurrently with gemcitabine)

The most common adverse reactions in pivotal study PA.3 in pancreatic cancer patients receiving Erlotinib Tablets 100 mg plus gemcitabine were fatigue, rash and diarrhoea. In the Erlotinib Tablets plus gemcitabine arm, Grade 3/4 rash and diarrhoea were each reported in 5% of patients. The median time to onset of rash and diarrhoea was 10 days and 15 days, respectively. Rash and diarrhoea each resulted in dose reductions in 2% of patients, and resulted in study discontinuation in up to 1% of patients receiving Erlotinib Tablets plus gemcitabine.

Table 1: ADRs occurring in ≥ 10% of patients in BR.21 (treated with Erlotinib Tablets) and PA.3 (treated with Erlotinib Tablets plus gemcitabine) studies and ADRs occurring more frequently (≥ 3%) than placebo in BR.21 (treated with Erlotinib Tablets) and PA.3 (treated with Erlotinib Tablets plus gemcitabine) studies

		Erlotinib (BR.21) N = 485		**Erlotinib (PA.3) N = 259**			**Frequency category of highest incidence**
NCI-CTC Grade	**Any Grade**	**3**	**4**	**Any Grade**	**3**	**4**	
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**	
Infections and infestations Infection*	24	4	0	31	3	<1	very common
Metabolism and nutrition disorders Anorexia Weight decreased	52 -	8 -	1 -	- 39	- 2	- 0	very common
Eye disorders	12	0	0	-	-	-	very common

Keratoconjunctivitis sicca				-	-	-	very common
Conjunctivitis	12	<1	0				
Psychiatric disorders Depression	-	-	-	19	2	0	very common very common
Nervous system disorders	-	-	-	13	1	<1	very
Neuropathy							
Headache	-	-	-	15	<1	0	common
Respiratory, thoracic and mediastinal disorders	41	17	11	- 16	- 0	- 0	very common
Dyspnoea							very
Cough	33	4	0				common
Gastrointestinal	54	6	<1	48	5	<1	very
				-	-	-	common
				-	-	-	very
				22	<1	0	common
				-	-	-	very
				17	<1	0	common
disorders				13	0	0	very
Diarrhoea**							common
Nausea	33	3	0				very
Vomiting	23	2	<1				common
Stomatitis	17	<1	0				very
Abdominal pain	11	2	<1				common
Dyspepsia	-	-	-				very
Flatulence	-	-	-				common
Skin and subcutaneous tissue disorders	75	8	<1	69	5	0	very
				-	-	-	common
				- 14	- 0	- 0	very
							common
							very
Rash***							common
Pruritus	13	<1	0				very
Dry skin	12	0	0				common
Alopecia	-	-	-				
General disorders and administration site conditions	52	14	4	73	14	2	very
	-	-	-	36	3	0	common
Fatigue Pyrexia Rigors	-	-	-	12	0	0	very common very common

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

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

*** Rash included dermatitis acneiform.

- corresponds to percentage below threshold.

Table 2: Summary of ADRs per frequency category:

Body System	**Very common (=1/10)**	**Common (=1/100 to <1/10)**	**Uncommon (=1/1,000 to <1/100)**	**Rare to <1/1,000)**	**Very rare (<1/10,000)**	**Not known8**
Eye disorders		-Keratitis - Conjunctivi tis1	-Eyelash changes 2		-Corneal perforations -Corneal ulcerations -Uveitis	
Respiratory, thoracic and mediastinal disorders		-Epistaxis	-Interstitial lung disease (ILD)3			
Gastrointestin al disorders	- Diarrhoea7	- Gastrointe stinal bleeding4, 7	- Gastrointestinal perforations7	-Pneumatosis intestinalis		
Hepato biliary disorders	-Liver function test abnormalit ies5			-Hepatic failure 6 -Hepatitis		-Acute hepatitis
Skin and subcutaneous tissue disorders	-Rash	-Alopecia -Dry skin1 - Paronychia -Folliculitis -Acne/ Dermatitis acneiform -Skin fissures	-Hirsutism -Eyebrow changes -Brittle and Loose nails -Mild skin reactions such as hyperpigmentat ion	-Palmar plantar erythrodys-aesthesia syndrome	-Stevens-Johnson syndrome/Toxic epidermal necrolysis7	
Renal and urinary disorders		-Renal insufficienc y1	-Nephritis1 -Proteinuria1			

5. How to store product

Store below 30°C.

6. Contents of the pack and other information

Tablets core:

Erlotinib Hydrochloride(Form-A) IH, Lactose Monohydrate (Super tab 11 SD), Microcrystalline Cellulose (Avicel PH 112), Sodium Starch Glycolate (Primojel), Magnesium stearate (LIGAMED MF-2-V), Sodium Lauryl Sulphate (STEPANOL WA-100), Magnesium stearate USP/NF (Ligamed MF-2-V1), Opadry White 20B580000 IH

Tablet coating

Opadry White 20B580000

Coating agent composition: Opadry White 20B580000, IH

%w/w	Ingredients/Compendial Reference	Grade/Dye Strength	E Number	CFR Reference	CI Number
35.000	HPMC 2910/Hypromellose (USP, Ph.Eur, JP, Ch.P)	6 mPas	E464	172.874	-
35.000	Hydroxypropyl Cellulose (NF, Ph.Eur, JP,FCC)	-	E463	172.87	-
20.000	Titanium Dioxide (USP,FCC, Ph.Eur, JP, Ch.P)	-	E171	73.575,73.15	77891
10.000	Macrogol/PEG (NF, FCC, Ph.Eur, JECFA, JP)	MW 400	E1521	172.820	-

What Erlotinib Hydrochloride Tablets looks like and contents of the pack

White coloured, round biconvex film coated tablets debossed with H on one side and ‘22’ on other side.

The Tablets are packed in

30's HDPE Container

Supplier and Manufacturer:

Supplier	Manufacturer
Hetero Labs Limited 7-2-A2, Hetero Corporate Industrial Estates Sanath Nagar, Hyderabad-500 018 Telangana, India Tel. No.: +91 40 23704923/ 24/25 Fax:+91 40 23704035, 23813359 Email:contact@heterodrugs.com	Hetero Labs Limited Unit-V, TSIIC Formulation SEZ, Survey No. 439, 440, 441 & 458, Polepally village, Jadcherla Mandal, Mahaboob Nagar (Dist) – 509301, Telangana. India.