

1. NAME OF THE MEDICINAL PRODUCT

Veiasu 250 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg of gefitinib.

Excipient with known effect:

Each tablet contains 163.5 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets (tablet).

Tablets are brown, round, biconvex, debossed with “LP 100” on one side and plain on the other side, with a size of 11.13±0.5 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gefitinib is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK (see section 4.4).

4.2 Posology and method of administration

Treatment with gefitinib should be initiated and supervised by a physician experienced in the use of anticancer therapies.

Posology

Gefitinib treatment should only be initiated by a medical specialist experienced in the treatment of patients with advanced NSCLC.

The recommended posology of gefitinib is one 250 mg tablet once a day. If a dose is missed, it should be taken as soon as the patient remembers. If it is less than 12 hours to the next dose, the patient should not take the missed dose. Patients should not take a double dose (two doses at the same time) to make up for a forgotten dose.

Gefitinib is not recommended for use in children or adolescents as safety and effectiveness in these patient populations has not been studied.

No dosage adjustment is required on the basis of patient age, body weight, gender, ethnicity, mild to moderate renal impairment or in patients with moderate to severe hepatic impairment due to liver metastases (see section 5.1).

Dosage adjustment: Patients with poorly tolerated diarrhoea or skin adverse drug reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg dose (see section 4.8).

In the event of acute onset or worsening of pulmonary symptoms (dyspnoea, cough, fever) gefitinib therapy should be interrupted and a prompt investigation of these symptoms should occur and

appropriate treatment initiated. If interstitial lung disease is confirmed, gefitinib should be discontinued and the patient treated appropriately.

Patients who develop onset of new eye symptoms such as pain should be medically evaluated and managed appropriately, including Gefitinib therapy interruption and removal of an aberrant eyelash if present. After symptoms and eye changes have resolved, the decision should be made concerning reinstatement of the 250 mg daily dose.

Method of administration

The tablet may be taken orally with or without food, at about the same time each day.

Where dosing of whole tablets is not possible, such as patients who are only able to swallow liquids, tablets may be administered as a dispersion in water. The tablet should be dropped into half a glass of drinking water (non-carbonated), without crushing, and the glass stirred until the tablet has dispersed (approximately 15 minutes) and the contents subsequently drunk immediately. The glass should be rinsed with a further half glass of water and the contents drunk. The liquid can also be administered via a nasogastric tube.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

When considering the use of gefitinib as first-line treatment for advanced or metastatic NSCLC, it is recommended that EGFR mutation assessment of the tumour tissue is attempted for all patients. When assessing the mutation status of a patient it is important that a well-validated and robust methodology is chosen to minimise the possibility of false negative or false positive determinations. Tumour samples which are used for the diagnosis of advanced NSCLC are the preferred sample type for EGFR mutation testing. A tumour sample should be collected and tested where possible. If a tumour sample is not available or evaluable, then circulating tumour DNA (ctDNA) obtained from a blood (plasma) sample may be used. Only robust, reliable, sensitive test(s) with demonstrated utility on ctDNA should be used for the determination of EGFR mutation status of ctDNA. It is not always possible to detect EGFR mutations using this sample type (0.2% false positives, 34.3% false negatives) (see section 5.1).

In the first line setting, gefitinib should not be used in preference to doublet chemotherapy in mutation-negative patients.

Interstitial Lung Disease (ILD), which may be acute in onset, has been observed in patients receiving gefitinib, and some cases have been fatal (see section 4.8). If patients present with worsening of respiratory symptoms such as dyspnoea, cough and fever, gefitinib should be interrupted and prompt investigation initiated. If ILD is confirmed, gefitinib should be discontinued and the patient treated appropriately.

In a Japanese pharmacoepidemiological case control study in 3,159 patients with NSCLC receiving gefitinib or chemotherapy who were followed up for 12 weeks, the following risk factors for developing ILD (irrespective of whether the patient received gefitinib or chemotherapy) were identified: smoking, poor performance status (PS \geq 2), CT scan evidence of reduced normal lung (\leq 50%), recent diagnosis of NSCLC ($<$ 6 months), pre-existing ILD, older age (\geq 55 years old) and concurrent cardiac disease. Risk of mortality among patients who developed ILD on gefitinib or chemotherapy was higher in patients with the following risk factors: smoking, CT scan evidence of reduced normal lung (\leq 50%), pre-existing ILD, older age (\geq 65 years old), and extensive areas adherent to pleura (\geq 50%).

Hepatotoxicity and liver impairment

Liver function test abnormalities (including increases in alanine aminotransferase, aspartate aminotransferase, bilirubin) have been observed, uncommonly presenting as hepatitis (see section 4.8).

There have been isolated reports of hepatic failure which in some cases led to fatal outcomes. Therefore, periodic liver function testing is recommended. Gefitinib should be used cautiously in the presence of mild to moderate changes in liver function. Discontinuation should be considered if changes are severe.

Cerebrovascular events have been reported in clinical studies of gefitinib. A relationship with gefitinib has not been established.

Substances that are inducers of CYP3A4 activity may increase metabolism and decrease gefitinib plasma concentrations. Therefore, co-medication with CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or St John's Wort) may reduce efficacy (see section 4.5).

International Normalised Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin (see section 4.5). Patients taking warfarin should be monitored regularly for changes in Prothrombin Time (PT) or INR.

Drugs that cause significant sustained elevation in gastric pH may reduce plasma concentrations of gefitinib and therefore may reduce efficacy (see section 4.5 and 5.1).

Patients should be advised to seek medical advice promptly in the event of developing:

- severe or persistent diarrhoea, nausea, vomiting or anorexia

These symptoms should be managed as clinically indicated (see section 4.8).

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 gefitinib should be interrupted, and if symptoms do not resolve, or recur on reintroduction of gefitinib, permanent discontinuation should be considered.

Gefitinib should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Recent corneal surgery and contact lens wearing are known to be independent risk factors for ocular toxicity including corneal erosion.

In a phase I/II trial of gefitinib and radiation in paediatric patients, newly diagnosed with brain stem glioma or incompletely resected supratentorial malignant glioma, 4 cases (1 fatal) of CNS haemorrhages were reported from 45 patients enrolled. A further case of CNS haemorrhage has been reported in a child with an ependymoma from a trial with gefitinib alone. An increased risk of cerebral haemorrhage in adult patients with NSCLC receiving gefitinib has not been established.

Phase II clinical trial data, where gefitinib and vinorelbine have been used concomitantly, indicate that gefitinib may exacerbate the neutropenic effect of vinorelbine.

Gastrointestinal perforation has been reported in patients taking gefitinib. In most cases this is associated with other known risk factors, including increasing age, concomitant medications such as steroids or NSAIDs, underlying history of GI ulceration, smoking or bowel metastases at sites of perforation.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies have shown that the metabolism of gefitinib is predominantly via CYP3A4.

Co-administration with rifampicin (a known potent CYP3A4 inducer) in healthy volunteers reduced mean gefitinib AUC by 83% of that without rifampicin (see section 4.4).

Co-administration with itraconazole (a CYP3A4 inhibitor) resulted in an 80% increase in the mean AUC of gefitinib in healthy volunteers. This increase may be clinically relevant since adverse experiences are related to dose and exposure. Although interaction studies with other CYP3A4 inhibitors have not been performed it is expected that drugs such as ketoconazole, clotrimazole, ritonavir would also inhibit gefitinib metabolism.

Co-administration of ranitidine at a dose that caused sustained elevations in gastric pH (≥ 5), resulted in a reduced mean gefitinib AUC by 47% in healthy volunteers (see section 4.4 and 5.1).

Other potential interactions

INR elevations and/or bleeding events have been reported in some patients concomitantly taking warfarin (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must be advised not to get pregnant during therapy.

Pregnancy

There are no data from the use of gefitinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. gefitinib should not be used during pregnancy unless clearly necessary.

Breastfeeding

It is not known whether gefitinib is secreted in human milk. Gefitinib and metabolites of gefitinib accumulated in milk of lactating rats (see section 5.3). Gefitinib is contraindicated during breast-feeding and therefore breast-feeding must be discontinued while receiving gefitinib therapy (see section 4.3).

4.7 Effects on ability to drive and use machines

During treatment with gefitinib, asthenia has been reported. Therefore, patients who experience this symptom should be cautious when driving or using machines.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs), occurring in more than 20% of the patients, are diarrhoea and skin reactions (including rash, acne, dry skin and pruritus). ADRs usually occur within the first month of therapy and are generally reversible. Approximately 10% of patients had a severe ADR (Common Toxicity Criteria, (CTC) grade 3 or 4). Approximately 3% of patients stopped therapy due to an ADR.

Adverse Drug Reactions (ADRs) have been assigned to the frequency categories in Table 1 where possible based on the incidence of comparable Adverse Event reports in a pooled dataset from the ISEL, INTEREST and IPASS phase III clinical trials (2462 gefitinib-treated patients). In assigning these frequencies no account was taken of the frequency of reports within the comparative treatment groups or whether the investigator considered it to be related to study medication.

Frequency of ADRs relating to abnormal laboratory values is based on patients with a 2 or more CTC grade change from baseline in the relevant laboratory parameters.

Tabulated list of adverse reactions

The safety profile presented in Table 1 is based on the gefitinib clinical development programme and post marketed experience. Adverse reactions have been assigned to the frequency categories in Table 1 where possible based on the incidence of comparable adverse event reports in a pooled dataset from the ISEL, INTEREST and IPASS phase III clinical trials (2462 gefitinib-treated patients).

Frequencies of occurrence of undesirable effects are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions

Adverse reactions by system organ class and frequency		
Metabolism and nutrition disorders	Very common	Anorexia mild or moderate (CTC grade 1 or 2).
Eye disorders	Common	Conjunctivitis, blepharitis, and dry eye*, mainly mild (CTC grade 1).
	Uncommon	Corneal erosion, reversible and sometimes in association with aberrant eyelash growth. Keratitis (0.12%).
Vascular disorders	Common	Haemorrhage, such as epistaxis and haematuria.
Respiratory, thoracic and mediastinal disorders	Common	Interstitial lung disease (1.3%), often severe (CTC grade 3-4). Cases with fatal outcomes have been reported.
Gastrointestinal disorders	Very common	Diarrhoea, mainly mild or moderate (CTC grade 1 or 2). Vomiting, mainly mild or moderate (CTC grade 1 or 2). Nausea, mainly mild (CTC grade 1). Stomatitis, predominantly mild in nature (CTC grade 1).
	Common	Dehydration, secondary to diarrhoea, nausea, vomiting or anorexia. Dry mouth*, predominantly mild (CTC grade 1).
	Uncommon	Pancreatitis. Gastrointestinal perforation.
Hepatobiliary disorders	Very common	Elevations in alanine aminotransferase, mainly mild to moderate.
	Common	Elevations in aspartate aminotransferase, mainly mild to moderate. Elevations in total bilirubin, mainly mild to moderate.
	Uncommon	Hepatitis**
Skin and subcutaneous tissue disorders	Very common	Skin reactions, mainly a mild or moderate (CTC grade 1 or 2) pustular rash, sometimes itchy with dry skin, including skin fissures, on an erythematous base.
	Common	Nail disorder. Alopecia. Allergic reactions (1.1%), including angioedema and urticarial.
	Rare	Bullous conditions including Toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme. Cutaneous vasculitis***.
Renal and urinary disorders	Common	Asymptomatic laboratory elevations in blood creatinine. Proteinuria. Cystitis.
	Rare	Haemorrhagic cystitis***.
General disorders and administration site conditions	Very common	Asthenia, predominantly mild (CTC grade 1).
	Common	Pyrexia.

The frequency of adverse drug reactions relating to abnormal laboratory values is based on patients with a change from baseline of 2 or more CTC grades in the relevant laboratory parameters.

* This adverse reaction can occur in association with other dry conditions (mainly skin reactions) seen with gefitinib.

** This includes isolated reports of hepatic failure which in some cases led to fatal outcomes.

*** It was not possible to assign frequencies for cutaneous vasculitis and haemorrhagic cystitis based on the Phase III studies as there were no reports of these reactions in trials in which they could have been detected, therefore frequencies are estimated based on European Commission Guidance (September 2009), which assumes there were 3 reports across the monotherapy studies.

From a phase III double blind clinical trial (1692 patients) comparing gefitinib plus best supportive care (BSC) to placebo plus BSC in patients with advanced NSCLC who had received 1 or 2 prior chemotherapy regimens and were refractory or intolerant to their most recent regimen, the incidence of ILD-type events in the overall population was similar, and approximately 1% in both treatment arms. The majority of ILD-type events reported were from patients of Oriental ethnicity and the ILD incidence among patients of Oriental ethnicity receiving gefitinib therapy and placebo was similar, approximately 3% and 4% respectively. One ILD-type event was fatal, and this occurred in a patient receiving placebo.

In a Post-Marketing Surveillance study in Japan (3350 patients) the reported rate of ILD-type events in patients receiving gefitinib was 5.8%.

In a Japanese Pharmacoepidemiological case control study(see section 4.4) in patients with NSCLC, the crude cumulative incidence of ILD (unadjusted for imbalances in patient characteristics) at 12 weeks follow-up was 4.0% in patients receiving gefitinib and 2.1% in those receiving chemotherapy and the adjusted odds ratio (OR) of developing ILD was 3.2 (95% confidence interval [CI] 1.9 to 5.4) for gefitinib versus chemotherapy. An increased risk of ILD on gefitinib relative to chemotherapy was seen predominantly during the first 4 weeks of treatment (adjusted OR 3.8; 95% CI 1.9 to 7.7); thereafter the relative risk was lower (adjusted OR 2.5; 95% CI 1.1 to 5.8).

In a phase III open-label clinical trial (IPASS) in 1217 patients comparing gefitinib to carboplatin/paclitaxel doublet chemotherapy as first-line treatment in selected patients with advanced NSCLC in Asia, the incidence of ILD-type events was 2.6% on the gefitinib treatment arm versus 1.4% on the carboplatin/paclitaxel treatment arm.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

There is no specific treatment in the event of overdose of gefitinib. Adverse reactions associated with overdose should be treated symptomatically; in particular severe diarrhoea should be managed as clinically indicated. In phase I clinical trials, a limited number of patients were treated with daily doses of up to 1000 mg. An increase of frequency and severity of some adverse reactions was observed, mainly diarrhoea and skin rash.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01XE02

Mechanism of action and pharmacodynamic effects

The epidermal growth factor (EGF) and its receptor (EGFR [HER1; ErbB1]) have been identified as key drivers in the process of cell growth and proliferation for normal and cancer cells. EGFR activating mutation within a cancer cell is an important factor in promotion of tumour cell growth, blocking of apoptosis, increasing the production of angiogenic factors and facilitating the processes of metastasis.

Gefitinib is a selective small molecule inhibitor of the epidermal growth factor receptor tyrosine kinase and is an effective treatment for patients with tumours with activating mutations of the EGFR tyrosine kinase domain regardless of line of therapy. No clinically relevant activity has been shown in patients with known EGFR mutation-negative tumours.

Clinical characteristics of never smoker, adenocarcinoma histology and female gender have been shown to be independent predictors of positive EGFR mutation status. Asian patients also have a higher incidence of EGFR mutation-positive tumours.

Resistance

Most NSCLC tumours with sensitising EGFR kinase mutations eventually develop resistance to gefitinib treatment, with a median time to disease progression of 1 year. In about 60% of cases, resistance is associated with a secondary T790M mutation for which T790M targeted EGFR TKIs may be considered as a next line treatment option. Other potential mechanisms of resistance that have been reported following treatment with EGFR signal blocking agents include: bypass signalling such as HER2 and MET gene amplification and PIK3CA mutations. Phenotypic switch to small cell lung cancer has also been reported in 5-10% of cases.

Clinical efficacy and safety

IPASS Study:

The randomised phase III first line IPASS study was conducted in patients in Asia¹ with advanced (stage IIIB or IV) NSCLC of adenocarcinoma histology who were ex-light smokers (ceased smoking >15 years ago and smoked <10 pack years) or never smokers (see Table 3).

¹China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan and Thailand.

Table 2 Efficacy outcomes for gefitinib versus carboplatin/paclitaxel from the IPASS study

Population	N	Objective response rates and 95% CI for difference between treatments ^a	Primary endpoint Progression free survival (PFS) ^{a,b}	Overall survival ^{a,b}
Overall	1217	43.0% vs 32.2% [5.3%, 16.1%]	HR 0.74 [0.65, 0.85] 5.7 m vs 5.8 m p<0.0001	HR 0.90 [0.79, 1.02] 18.8 m vs 17.4 m p=0.1087
EGFR mutation-positive	261	71.2% vs 47.3% [12.0%, 34.9%]	HR 0.48 [0.36, 0.64] 9.5 m vs 6.3 m p<0.0001	HR 1.00 [0.76, 1.33] 21.6 m vs 21.9 m
EGFR mutation-negative	176	1.1% vs 23.5% [-32.5%, -13.3%]	HR 2.85 [2.05, 3.98] 1.5 m vs 5.5 m p<0.0001	HR 1.18 [0.86, 1.63] 11.2 m vs 12.7 m
EGFR mutation-unknown	780	43.3% vs 29.2% [7.3%, 20.6%]	HR 0.68 [0.58 to 0.81] 6.6 m vs 5.8 m p<0.0001	HR 0.82 [0.70 to 0.96] 18.9 m vs. 17.2 m

^a Values presented are for gefitinib versus carboplatin/paclitaxel.

^b “m” is medians in months. Numbers in square brackets are 95% confidence intervals for HR

NR Not reached.

N Number of patients randomised.

HR Hazard ratio (hazard ratios <1 favour gefitinib)

Pre-planned exploratory analyses were conducted on the biomarker data at the time of the primary analysis. A total of 437 patients had evaluable data for EGFR mutation analysis. PFS was significantly longer for gefitinib than carboplatin/paclitaxel in EGFR mutation positive patients (n=261, HR 0.48, 95% CI 0.36 to 0.64, p<0.0001), and significantly longer for carboplatin/paclitaxel than gefitinib in EGFR mutation negative patients (n=176, HR 2.85, 95% CI 2.05 to 3.98, p<0.0001). Patients were considered EGFR mutation positive if one of 29 EGFR mutations was detected by Amplification Refractory Mutation System (ARMS) using DxS EGFR 29 mutation detection kit. Patients were deemed EGFR mutation negative if samples were successfully analysed and none of the 29 EGFR mutations was detected. PFS results in the subgroup with unknown EGFR-mutation status (hazard ratio with gefitinib, 0.68; 95% CI, 0.58 to 0.81; P<0.0001) were similar to those for the overall population.

In EGFR mutation positive patients, ORR was superior for gefitinib (71.2%) vs carboplatin/paclitaxel (47.3%) (OR 2.751, 95% CI 1.646 to 4.596, p=0.0001). In EGFR mutation negative patients, ORR was superior for carboplatin/paclitaxel (23.5%) vs gefitinib (1.1%) (OR 0.036, 95% CI 0.005 to 0.273, p=0.0013).

Quality of life outcomes differed according to EGFR mutation status. In EGFR mutation-positive patients, significantly more gefitinib-treated patients experienced an improvement in quality of life and lung cancer symptoms vs carboplatin/paclitaxel (see Table 4).

Table 3 Quality of life outcomes for gefitinib versus carboplatin/paclitaxel from the IPASS study

Population	N	FACT-L QoL improvement rate ^a %	LCS symptom improvement rate ^a %
Overall	1151	(48.0% vs 40.8%) p=0.0148	(51.5% vs 48.5%) p=0.3037
EGFR mutation-positive	259	(70.2% vs 44.5%) p<0.0001	(75.6% vs 53.9%) p=0.0003
EGFR mutation-negative	169	(14.6% vs 36.3%) p=0.0021	(20.2% vs 47.5%) p=0.0002

Trial outcome index results were supportive of FACT-L and LCS results

^a Values presented are for gefitinib versus carboplatin/paclitaxel.

N Number of patients evaluable for quality of life analyses

QoL Quality of life

FACT-L Functional assessment of cancer therapy-lung

LCS Lung cancer subscale

An analysis of overall survival (OS) was performed after 954 deaths (78% maturity), which demonstrated no statistically significant difference in OS for gefitinib versus carboplatin/paclitaxel in the overall study population (HR 0.901, 95% CI 0.793 to 1.023; p=0.1087). Median OS: gefitinib, 18.8 months; carboplatin/paclitaxel, 17.4 months.

Subgroup analyses of OS by EGFR mutation status showed no significant difference in OS for gefitinib versus carboplatin/paclitaxel in the subgroup of patients with known mutation positive (HR 1.002, 95% CI 0.756 to 1.328; median OS 21.6 months vs. 21.9 months) or negative (HR 1.181, 95% CI 0.857 to 1.628; median OS 11.2 months vs. 12.7 months) tumours. The OS outcome in the subgroup of patients with unknown mutation status (HR 0.818, 95% CI 0.696 to 0.962; median OS 18.9 months vs. 17.2 months) was consistent with the overall population.

In the IPASS trial, gefitinib demonstrated superior PFS, ORR, QoL and symptom relief with no significant difference in overall survival compared to carboplatin/paclitaxel in previously untreated patients, with locally advanced or metastatic NSCLC, whose tumours harboured activating mutations of the EGFR tyrosine kinase.

ISEL Study:

In a phase III double blind clinical trial comparing gefitinib to placebo in patients with advanced NSCLC who had received 1 or 2 chemotherapy regimens, gefitinib did not significantly prolong survival in the overall population (HR 0.89, CI 0.77 to 1.02, p=0.09, Median 5.6 vs 5.1 months for gefitinib and placebo respectively), or in patients with adenocarcinoma (HR 0.84, CI 0.68 to 1.03, p=0.09, Median 6.3 vs 5.4 months for gefitinib and placebo respectively). Gefitinib also did not produce any significant benefits in terms of quality of life or symptom control. Pre-planned subgroup analyses showed a statistically significant increase in survival for patients of Oriental ethnicity treated with gefitinib compared to placebo (HR=0.66, CI 0.48 to 0.91, p=0.01, Median 9.5 vs 5.5 months), and for patients that had never smoked treated with gefitinib compared to placebo (HR=0.67, CI 0.49 to 0.92, p=0.01, Median 8.9 vs 6.1 months).

In patients with high EGFR copy number (n=114) there was a non-significant trend towards improved survival in patients receiving gefitinib compared to those receiving placebo (HR 0.61, 95% CI 0.36 to 1.04, p=0.067). Analysis of EGFR gene copy number was measured by fluorescence in situ hybridisation (FISH) using the LSI EGFR SpectrumOrange/CEP 7 SpectrumGreen probe. Patients were considered to have high EGFR gene copy if their tumour had high polysomy (≥ 4 copies in $\geq 40\%$ of cells) or gene amplification (presence of tight EGFR gene clusters and a ratio of gene/chromosome per cell ≥ 2 , or ≥ 15 copies of EGFR per cell in $\geq 10\%$ of analysed cells).

Analysis of EGFR protein expression data showed that EGFR positive patients had no significant survival benefits when treated with gefitinib compared to placebo (N=264, HR=0.77; CI 0.56 to 1.08, p=0.13) than EGFR negative patients (N=115, HR=1.57; CI 0.86 to 2.87, p=0.14), though neither of the subset analyses were statistically significant. EGFR status was not tested for the majority of patients. For patients in whom EGFR status was not tested (N=1313, HR=0.84; CI 0.73 to 0.98, p=0.03), the HR was similar to that seen in the overall study population as would be expected. A positive EGFR expression status was defined as having at least 10% of cells staining for EGFR in contrast to the 1% cut-off specified in the DAKO EGFR pharmDx™ kit instructions.

For patients with an EGFR gene mutation, there was insufficient data to allow a meaningful evaluation of survival.

The overall trial data suggest that the patients most likely to benefit from treatment with gefitinib are patients of Oriental ethnicity or patients who have never smoked.

IFUM Study:

The IFUM study was a single-arm, multicentre study conducted in Caucasian patients (n=106) with activating, sensitizing EGFR mutation positive NSCLC to confirm that the activity of gefitinib is similar in Caucasian and Asian populations. The ORR according to investigator review was 70% and the median PFS was 9.7 months. These data are similar to those reported in the IPASS study.

Circulating Tumour DNA (ctDNA)

In the IFUM trial, mutation status was assessed in tumour and ctDNA samples derived from plasma, using the Therascreen EGFR RGQ PCR kit (Qiagen). Both ctDNA and tumour samples were evaluable for 652 patients out of 1060 screened. The sensitivity of EGFR mutation testing in ctDNA using the Qiagen Therascreen EGFR RGQ PCR kit was 65.7%, with a specificity of 99.8%. The positive and negative predictive values of ctDNA were 98.6% and 93.8%, respectively (Table 4). Objective response rate in the IFUM full analysis set of patients who were ctDNA positive was 69.8% (95% CI: 60.5% to 77.7%). The ORR in those patients who were tumour and ctDNA mutation positive was 76.9% (95% CI: 65.4% to 85.5%) and in those who were tumour only mutation positive but ctDNA negative 59.5% (95% CI: 43.5% to 73.3%).

Table 4 Summary of baseline mutation for tumour and ctDNA samples in all screened patients evaluable for both samples

Measure	Definition	IFUM Rate %(CI)	IFUM N

Proportion of Concordance	Number of times that the ctDNA and tumour results agree	94.3 (92.3, 96.0)	652
Sensitivity	Proportion of tumour M+ that are M+ by ctDNA	65.7 (55.8, 74.7)	105
Specificity	Proportion of tumour M- that are M- by ctDNA	99.8 (99.0, 100.0)	547
Positive Predictive Value	Proportion of ctDNA M+ that are M+ by tumour	98.6 (92.3, 100.0)	70
Negative Predictive Value	Proportion of ctDNA M- that are M- by tumour	93.8 (91.5, 95.6)	582

These data are consistent with the pre-planned exploratory Japanese subgroup analysis in IPASS. In that study ctDNA derived from serum, not plasma was used for EGFR mutation analysis using the EGFR Mutation Test Kit (DxS) (N= 86). In that study, concordance was 66%, sensitivity was 43.1 %, specificity was 100%. The positive and negative predictive values were 100% and 54.7%, respectively.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of gefitinib, absorption is moderately slow and peak plasma concentrations of gefitinib typically occur at 3 to 7 hours after administration. Mean absolute bioavailability is 59% in cancer patients. Exposure to gefitinib is not significantly altered by food. In a trial in healthy volunteers where gastric pH was maintained above pH 5, gefitinib exposure was reduced by 47%, likely due to impaired solubility of gefitinib in the stomach (see sections 4.4 and 4.5).

Distribution

Gefitinib has a mean steady-state volume of distribution of 1400 l indicating extensive distribution into tissue. Plasma protein binding is approximately 90%. Gefitinib binds to serum albumin and alpha 1-acid glycoprotein.

In vitro data indicate that gefitinib is a substrate for the membrane transport protein P-gp.

Biotransformation

In vitro data indicate that CYP3A4 is the major P450 isozyme involved in the oxidative metabolism of gefitinib.

In vitro studies have shown that gefitinib has limited potential to inhibit CYP2D6. In a clinical trial in patients, gefitinib was co-administered with metoprolol (a CYP2D6 substrate). This resulted in a small (35%) increase in exposure to metoprolol, which is not considered to be clinically relevant.

Gefitinib shows no enzyme induction effects in animal studies and no significant inhibition (*in vitro*) of any other cytochrome P450 enzyme.

Three sites of biotransformation have been identified in the metabolism of gefitinib: metabolism of the N-propylmorpholino-group, demethylation of the methoxy- substituent on the quinazoline and oxidative defluorination of the halogenated phenyl group. Five metabolites have been fully identified in faecal extracts and the major component was O-desmethyl gefitinib, although this only accounted for 14% of the dose.

In human plasma 8 metabolites were fully identified. The major metabolite identified was O-desmethyl gefitinib, which was 14-fold less potent than gefitinib at inhibiting EGFR stimulated cell

growth and had no inhibitory effect on tumour cell growth in mice. It is therefore considered unlikely that it contributes to the clinical activity of gefitinib.

The production of O-desmethyl gefitinib has been shown, in vitro, to be via CYP2D6. The role of CYP2D6 in the metabolic clearance of gefitinib has been evaluated in a clinical trial in healthy volunteers genotyped for CYP2D6 status. In poor metabolisers, no measurable levels of O-desmethyl gefitinib were produced. The range of gefitinib exposures achieved in both the extensive and the poor metaboliser groups were wide and overlapping but the mean exposure to gefitinib was 2-fold higher in the poor metaboliser group. The higher average exposures that could be achieved by individuals with no active CYP2D6 may be clinically relevant since adverse experiences are related to dose and exposure.

Elimination

Gefitinib is excreted mainly as metabolites via the faeces, with renal elimination of gefitinib and metabolites accounting for less than 4% of the administered dose.

Gefitinib total plasma clearance is approximately 500 ml/min and the mean terminal half-life is 41 hours in cancer patients. Administration of gefitinib once daily results in 2- to 8-fold accumulation, with steady-state exposures achieved after 7 to 10 doses. At steady-state, circulating plasma concentrations are typically maintained within a 2- to 3-fold range over the 24-hour dosing interval.

Special populations

From analyses of population pharmacokinetic data in cancer patients, no relationships were identified between predicted steady-state trough concentration and patient age, body weight, gender, ethnicity or creatinine clearance (above 20 ml/min).

Hepatic impairment

In a phase I open-label study of single dose gefitinib 250 mg in patients with mild, moderate or severe hepatic impairment due to cirrhosis (according to Child-Pugh classification), there was an increase in exposure in all groups compared with healthy controls. An average 3.1-fold increase in exposure to gefitinib in patients with moderate and severe hepatic impairment was observed. None of the patients had cancer, all had cirrhosis and some had hepatitis. This increase in exposure may be of clinical relevance since adverse experiences are related to dose and exposure to gefitinib.

Gefitinib has been evaluated in a clinical trial conducted in 41 patients with solid tumours and normal hepatic function, or moderate or severe hepatic impairment (classified according to baseline Common Toxicity Criteria grades for AST, alkaline phosphatase and bilirubin) due to liver metastases. It was shown that following daily administration of 250 mg gefitinib, time to steady-state, total plasma clearance (C_{maxSS}) and steady-state exposure (AUC_{24SS}) were similar for the groups with normal and moderately impaired hepatic function. Data from 4 patients with severe hepatic impairment due to liver metastases suggested that steady-state exposures in these patients are also similar to those in patients with normal hepatic function.

5.3 Preclinical safety data

Gefitinib showed no genotoxic potential.

There was, as expected from the pharmacological activity of gefitinib, a reduction in female fertility in the rat at a dose of 20 mg/kg/day. When administered during organogenesis, there were no effects on rat embryofetal development at the highest dose (30 mg/kg/day), however in the rabbit, there were reduced foetal weights at 20 mg/kg/day and above. There were no compound induced malformations in either species. When dosed to the rat throughout gestation and parturition, there was a reduction in pup survival at a dose of 20 mg/kg/day (see section 4.6).

Following oral administration of carbon-14 labelled gefitinib to rats 14 days post partum, concentrations of radioactivity in milk were higher than in blood (see section 4.6).

Data from nonclinical (*in vitro*) studies indicate that gefitinib has the potential to inhibit the cardiac action potential repolarization process (e.g. QT interval). Clinical experience has not shown a causal association between QT prolongation and gefitinib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Cellulose, microcrystalline (E460)
Croscarmellose sodium (E466)
Povidone K-30 (E1201)
Sodium laurilsulfate
Magnesium stearate

Tablet coating

Poly (vinyl alcohol) (E1203)
Macrogol 3350 (E1521)
Talc (E553b)
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to outer carton.

6.4 Special precautions for storage

Please refer to outer carton.

6.5 Nature and contents of container

PVC/PE/PVDC-Al unit-dose blisters containing 10 tablets. Three blisters are combined in a PET/Al/PE pouch, in a carton.
Pack size of 30 film-coated tablets.

6.6 Special precautions for disposal

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

7. PRODUCT OWNER

LOTUS INTERNATIONAL PTE. LTD.
80 Robinson Road
#02-00
Singapore 068898

8. DATE OF REVISION OF THE TEXT

05/2020