INGEFITINIB FILM COATED TABLET 250 MG

PRESENTATION

Brown, round, biconvex, film-coated tablet impressed with “250” on one side and plain on the other. Each tablet contains 250 mg gefitinib.

INDICATIONS

INGEFITINIB is indicated for the treatment of patients with locally advanced or metastatic Non Small Cell Lung Cancer (NSCLC) who have activating mutations of the EGFR TK.

DOSAGE AND ADMINISTRATION

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

The recommended dose of INGEFITINIB is one 250 mg tablet once a day, taken with or without food. If a dose of INGEFITINIB 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.

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.

INGEFITINIB 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 'PHARMACOKINETIC PROPERTIES' section).

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 'POSSIBLE ADVERSE REACTIONS' section).

In the event of acute onset or worsening of pulmonary symptoms (dyspnoea, cough, fever) INGEFITINIB therapy should be interrupted and a prompt investigation of these symptoms should occur and appropriate treatment initiated. If interstitial lung disease is confirmed, INGEFITINIB 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 INGEFITINIB 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.

CONTRAINDICATIONS

Known severe hypersensitivity to the active substance or to any of the excipients of this product.

WARNINGS AND PRECAUTIONS

When considering the use of INGEFITINIB 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 'PHARMACODYNAMICS PROPERTIES' section).

In the first line setting, INGEFITINIB 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 'POSSIBLE ADVERSE REACTIONS' section). If patients present with worsening of respiratory symptoms such as dyspnoea, cough and fever, INGEFITINIB should be interrupted and prompt investigation initiated. If ILD is confirmed, INGEFITINIB should be discontinued and the patient treated appropriately.

In a Japanese Pharmacoepidemiological case control study (see 'POSSIBLE ADVERSE REACTIONS' section) in 3159 patients with NSCLC who were followed up for 12 weeks when receiving gefitinib or chemotherapy, the following risk factors for developing ILD (irrespective of whether the patient received gefitinib or chemotherapy) were identified: smoking, poor performance status (PS ≥ 2), CT scan evidence of reduced normal lung (≤ 50%), recent diagnosis of NSCLC (< 6 months), pre-existing ILD, increasing age (≥ 55 years old) and concurrent cardiac disease. Risk of mortality among patients who developed ILD on both treatments was higher in patients with the following risk factors: smoking, CT scan evidence of reduced normal lung (≤ 50%), pre-existing ILD, increasing age (≥ 65 years old), and extensive areas adherent to pleura (≥ 50%).

Liver function test abnormalities (including increases in alanine aminotransferase, aspartate aminotransferase, bilirubin) have been observed (see 'POSSIBLE ADVERSE REACTIONS' section), uncommonly presenting as hepatitis. There have been isolated reports of hepatic failure which in some cases led to fatal outcomes. Therefore, periodic liver function testing is recommended. INGEFITINIB 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 'INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION' sections).

International Normalised Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin (see 'INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION' section). 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 'INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION' and 'PHARMACOKINETIC PROPERTIES' sections).

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 'POSSIBLE ADVERSE REACTIONS' section).

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

INGEFITINIB 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.

INGEFITINIB should be used with caution in patients with lactose intolerance.

See also ‘PREGNANCY AND LACTATION’ and ‘EFFECTS ON ABILITY TO DRIVE AND USE MACHINES’ sections.

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 ‘WARNINGS AND PRECAUTIONS’ section).

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, ritonovir 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 'WARNINGS AND PRECAUTIONS' and 'PHARMACOKINETIC PROPERTIES' sections).

INR elevations and/or bleeding events have been reported in some patients taking warfarin (see 'WARNINGS AND PRECAUTIONS' section).

PREGNANCY AND LACTATION

There are no data from the use of gefitinib in pregnant or breast-feeding women. Studies in animals have shown reproductive toxicity. Animal studies also indicate that gefitinib and certain metabolites pass into rat's breast-milk (see 'PRE-CLINICAL SAFETY DATA RELEVANT TO THE PRESCRIBER' section).

Women of childbearing potential must be advised to avoid becoming pregnant, and breast-feeding mothers must be recommended to discontinue nursing while receiving INGEFITINIB therapy.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

During treatment with gefitinib, asthenia has been reported and those patients who experience this symptom should observe caution when driving or using machines.

POSSIBLE ADVERSE REACTIONS

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.

Table 1 Adverse drug reactions by system organ class and frequency

MedDRA SOC	CIOMS descriptor / Overall frequency (All CTC grades)	Adverse drug reaction
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 or 4). Cases with fatal outcomes have been reported
Gastrointestinal disorders	Very Common	Diarrhoea, mainly mild or moderate (CTC grade 1 or 2) and less commonly, severe (CTC grade 3 or 4)
		Vomiting, mainly mild or moderate (CTC grade 1 or 2)
		Nausea, mainly mild (CTC grade 1)
		Stomatitis, predominantly mild (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 urticaria
	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 frequencies of adverse drug reactions relating to abnormal laboratory values are 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 ’WARNING AND PRECAUTIONS’ section) 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 (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.

OVERDOSE

There is no specific treatment in the event of overdose of INGEFITINIB. 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Gefitinib is a selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, commonly expressed in solid human tumours of epithelial origin. Inhibition of EGFR tyrosine kinase activity inhibits tumour growth, metastasis and angiogenesis and increases tumour cell apoptosis.

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 sensitizing 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 have been reported following treatment with EGFR signal blocking agents including 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.

IPASS Study:

The randomised phase III first line IPASS study was conducted in patients in Asia[1] 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 2).

[1] China, 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[ab]**	**Overall survival[abc]**
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 0.91 [0.76, 1.10] 18.6 m vs 17.3 m
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 0.78 [0.50, 1.20] NR vs 19.5 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 1.38 [0.92, 2.09] 12.1 m vs 12.6 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.
[c] From early analysis, overall survival follow up is ongoing
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 gefinitib (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 3).

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 mutationnegative	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 ≥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 ≥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^{TM} 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 INGEFITINIB 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 accordingto 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 tDNA 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.

Pharmacokinetic properties

Following intravenous administration, gefitinib is rapidly cleared, extensively distributed and has a mean elimination half-life of 48 hours. Following oral dosing in cancer patients, absorption is moderately slow and the mean terminal half-life is 41 hours. 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.

Absorption:

Following oral administration of gefitinib, peak plasma concentrations of gefitinib typically occur at 3 to 7 hours after dosing. 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% (see 'WARNINGS AND PRECAUTIONS' and 'INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION' sections).

Distribution:

Mean volume of distribution at steady state of gefitinib is 1400L indicating extensive distribution into tissue. Plasma protein binding is approximately 90%. Gefitinib binds to serum albumin and α1-acid glycoprotein.

Metabolism:

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 methoxysubstituent 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 total plasma clearance is approximately 500 mL/min. Excretion is predominantly via the faeces with renal elimination of drug and metabolites accounting for less than 4% of the administered dose.

Special populations:

In population based data analyses in cancer patients, no relationships were identified between predicted steady state trough concentration and patient age, body weight, gender, ethnicity or creatinine clearance.

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 dysfunction due to liver metastases. It was shown that following daily dosing of 250 mg gefitinib, time to steady state, total plasma clearance and steady state exposure ($C_{max,ss}$, $AUC_{24,ss}$) were similar for the groups with normal and moderately impaired hepatic function. Data from 4 patients with severe hepatic dysfunction due to liver metastases suggested that steady state exposures in these patients are also similar to those in patients with normal hepatic function.

PRE-CLINICAL SAFETY DATA RELEVANT TO THE PRESCRIBER

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 'PREGNANCY AND LACTATION' section).

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 'PREGNANCY AND LACTATION' section).

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.

A 2 year carcinogenicity study in rats resulted in a small but statistically significant increased incidence of hepatocellular adenomas in both male and female rats and mesenteric lymph node haemangiosarcomas in female rats at the highest dose (10 mg/kg/day) only. The hepatocellular adenomas were also seen in a 2 year carcinogenicity study in mice, which demonstrated a small increased incidence of this finding in male mice dosed at 50 mg/kg/day, and in both male and female mice at the highest dose of 90 mg/kg/day (reduced from 125 mg/kg/day from week 22). The effects reached statistical significance for the female mice, but not for the males. The clinical relevance of these findings is unknown.

PHARMACEUTICAL PARTICULARS

List of excipients

Core
Cellulose, microcrystalline (E460)
Lactose monohydrate
Croscarmellose sodium (E468)
Povidone (E1201)
Sodium laurilsulfate
Magnesium stearate (E470b)

Coating
Poly (vinyl alcohol) (E1203)
Macrogol (E1521)
Titanium dioxide (E171)
Talc (E553b)
Iron oxide red (E172)
Iron oxide yellow (E172)

Special precautions for storage
Do not store above 30°C. Store in the original package.

Shelf-life
Please refer to expiry date on the blister strip or outer carton.

Nature and contents of container
Aluminium-OPA/Alu/PVC blisters, 30 tablets

Product Registrant
Intega Pte Ltd
10 Anson Road #27-15
International Plaza
Singapore 079903

Manufacturer
Remedica Ltd
Aharnon Street, Limassol Industrial Estate,
3056 Limassol
Cyprus

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