

IRESSA® 250mg Film-coated Tablet

Trade Mark

PRESENTATION

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

INDICATIONS

IRESSA 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 ‘WARNINGS AND PRECAUTIONS’ section).

DOSAGE AND ADMINISTRATION

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

IRESSA 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 or renal function 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).

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 IRESSA as first-line treatment for locally 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. EGFR mutations identified in ctDNA are highly predictive of EGFR mutation positive tumours. However it is not always possible to detect EGFR mutations using this sample type (0.2% false positives, 34.3% false negatives), (see 'PHARMACODYNAMICS PROPERTIES' sections).

Interstitial Lung Disease (ILD), which may be acute in onset, has been observed in patients receiving IRESSA, 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, IRESSA should be interrupted and prompt investigation initiated. If ILD is confirmed, IRESSA 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 IRESSA or chemotherapy, the following risk factors for developing ILD (irrespective of whether the patient received IRESSA 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, 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 ($\leq 50\%$), pre-existing ILD, increasing age (≥ 65 years old), and extensive areas adherent to pleura ($\geq 50\%$).

Liver function test abnormalities (including increase 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. IRESSA should be used cautiously in the presence of mild to moderate change in liver function. Discontinuation should be considered if changes are severe.

Cerebrovascular events have been reported in clinical studies of IRESSA. A relationship with IRESSA 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' section).

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

In a phase I/II trial of IRESSA 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 IRESSA alone. An increased risk of cerebral haemorrhage in adult patients with NSCLC receiving IRESSA has not been established.

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

Gastrointestinal perforation has been reported in patients taking IRESSA. 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.

Also see section PREGNANCY AND LACTATION and EFFECTS ON ABILITY TO DRIVE AND USE MACHINES.

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.

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 IRESSA in pregnant or breast-feeding women. Studies in animals have shown reproductive toxicity. Animal studies also indicate that gefitinib and certain metabolites pass into rats 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 IRESSA therapy.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

During treatment with IRESSA, 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 diarrhea, 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 the table below 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 IRESSA-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
	Uncommon	Palmar-plantar erythrodysaesthesia syndrome
	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 IRESSA 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 IRESSA 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 IRESSA was 5.8%.

In a Japanese Pharmacoepidemiological case control study (see 'WARNINGS 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 IRESSA 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 IRESSA versus chemotherapy. An increased risk of ILD on IRESSA 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 IRESSA 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 IRESSA treatment arm versus 1.4% on the carboplatin/paclitaxel treatment arm.

OVERDOSE

There is no specific treatment in the event of overdose of IRESSA. 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. In one study a limited number of patients were treated weekly with doses from 1500 mg to 3500 mg. In this study IRESSA exposure did not increase with increasing dose, adverse events were mostly mild to moderate in severity, and were consistent with the known safety profile of IRESSA.

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.

Patients that have never smoked, have adenocarcinoma histology, are female gender or are of Asian ethnicity, are more like to benefit from treatment with IRESSA. These clinical characteristics are also associated with a higher rate of EGFR mutation positive tumours.

Resistance

Most NSCLC tumours with sensitizing EGFR kinase mutations eventually develop resistance to IRESSA 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 signaling 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:

In a phase III clinical trial conducted in Asia in 1217 patients with advanced (stage IIIB or IV) NSCLC of adenocarcinoma histology who were ex-light (ceased smoking > 15 years ago and smoked < 10 pack years) or never smokers and had not received previous chemotherapy, IRESSA was proven to be superior to carboplatin (AUC 5.0 or

6.0)/paclitaxel (200 mg/m²) in terms of Progression Free Survival (PFS) (Hazard Ratio [HR] 0.741, 95% CI 0.651 to 0.845, $p < 0.0001$) which was the primary endpoint of the trial. The effect was not constant over time, initially favouring carboplatin/paclitaxel and then favouring IRESSA, driven by differences in PFS outcomes by EGFR mutation status. EGFR mutation status was a strong predictive biomarker for the effect of IRESSA compared to carboplatin/paclitaxel.

Objective Response Rates (ORR) were superior for IRESSA (43.0%) vs. carboplatin/paclitaxel (32.2%) (Odds Ratio [OR] 1.59, 95% CI 1.25 to 2.01, $p = 0.0001$). Significantly more IRESSA-treated patients experienced a clinically important improvement in Quality of Life (QOL) vs. carboplatin/paclitaxel (Functional Assessment of Cancer Therapy for Lung Cancer [FACT-L] total score; 48% vs. 41%, OR 1.34, 95% CI 1.06 to 1.69, $p = 0.0148$; Trial Outcome Index [TOI]) 46% vs. 33%, OR 1.78, 95% CI 1.40 to 2.26, $p < 0.0001$). Similar proportions of patients on both treatments experienced an improvement in lung cancer symptoms (FACT-L Lung Cancer Subscale [LCS]) 52% for IRESSA vs. 49% for carboplatin/paclitaxel (OR 1.13, 95% CI 0.90 to 1.42, $p = 0.3037$).

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 IRESSA 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 IRESSA 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 IRESSA (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. IRESSA (1.1%) (OR 0.036, 95% CI 0.005 to 0.273, $p = 0.0013$).

In EGFR mutation positive patients, significantly more IRESSA treated patients experienced an improvement in QOL and lung cancer symptoms vs. carboplatin/paclitaxel (FACT-L total score; 70.2% vs. 44.5%, $p < 0.0001$) (TOI 70.2% vs. 38.3%, $p < 0.0001$) (LCS 75.6% vs. 53.9%, $p = 0.0003$). In EGFR mutation negative patients, significantly more carboplatin/paclitaxel treated patients experienced an improvement in QOL and lung cancer symptoms vs. IRESSA (FACT-L total score; 36.3% vs. 14.6%, $p = 0.0021$) (TOI 28.8% vs. 12.4%, $p = 0.0111$), (LCS 47.5% vs. 20.2%, $p = 0.0002$).

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

Subgroup analyses of OS by EGFR mutation status showed no significant difference in OS for IRESSA 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, IRESSA 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.

INTEREST Study:

In a phase III clinical trial of 1466 patients with locally advanced or metastatic NSCLC who had previously received platinum-based chemotherapy and were eligible for further chemotherapy, IRESSA was proven to be non-inferior to docetaxel (75 mg/m²) in terms of overall survival (Hazard Ratio [HR] 1.020, 96% Confidence Interval [CI] 0.905 to 1.150 [CI entirely below non-inferiority limit of 1.154], median 7.6 vs. 8.0 months).

IRESSA also had similar Progression-Free Survival (HR 1.04, 95% CI 0.93 to 1.18, p = 0.466, median 2.2 vs. 2.7 months) and similar Objective Response Rates (9.1% vs. 7.6%, odds ratio [OR] 1.22, 95% CI 0.82 to 1.84, p = 0.3257) compared to docetaxel. Significantly more IRESSA-treated patients experienced clinically important improvements in QOL compared with docetaxel (Functional Assessment of Cancer Therapy for Lung Cancer [FACTL] Trial Outcome Index [TOI]: 17% vs. 10%, p = 0.0026; FACT-L total score: 25% vs. 15%, p < 0.0001). Similar proportions of patients on both treatments experienced an improvement in lung cancer symptoms (FACT-L Lung Cancer Subscale [LCS] 20% vs. 17%, p = 0.1329).

The co-primary analysis evaluating overall survival in 174 patients with high EGFR gene copy number did not demonstrate superiority of IRESSA over docetaxel. Survival outcomes in patients with high EGFR gene copy number were similar for both treatments (HR 1.087, 95% CI 0.782 to 1.510, p = 0.6199, median 8.4 vs. 7.5 months).

ISEL Study:

In a phase III double blind clinical trial of 1692 patients comparing IRESSA plus 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, IRESSA 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 IRESSA 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 IRESSA and placebo respectively). Pre-planned subgroup analyses showed a statistically significant increase in survival for patients of Oriental ethnicity treated with IRESSA 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 IRESSA compared to placebo (HR = 0.67, CI 0.49 to 0.92, p = 0.01, Median 8.9 vs. 6.1 months).

Exploratory analysis of EGFR gene copy number data showed that the treatment effect, IRESSA compared to placebo, on survival was larger in patients with high EGFR gene copy number compared to patients with low EGFR gene copy number (interaction p-value = 0.0448). The hazard ratio, IRESSA to placebo, in patients with high EGFR gene copy number was 0.61 (N = 114; 95% CI 0.36 to 1.04, p = 0.067) and the hazard ratio in patients with low EGFR gene copy number was 1.16 (N = 256; 95% CI 0.81 to 1.64, p = 0.42). For patients in whom EGFR gene copy number was not tested (N = 1322, HR = 0.85, CI 0.73 to 0.99, p = 0.032), the HR was similar to that seen for the overall study population as would be expected.

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. 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 2). Objective response rate in the IFUM FAS population was 69.8% (95% CI: 60.5% to 77.7%). The ORR in those patients within the FAS population who were ctDNA mutation positive was 77.3% (95% CI: 65.8 to 85.7).

Table 2 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 IRESSA, 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 1400 L indicating extensive distribution into tissue. Plasma protein binding is approximately 90%. Gefitinib binds to serum albumin and α 1-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 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 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 250mg 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 IRESSA, time to steady state, total plasma clearance and steady state exposure ($C_{\max SS}$, AUC_{24SS}) 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

Special precautions for storage

Do not store above 30°C. Store in the original package.

Shelf-life

Please refer to outer carton for expiry date.

Pack size

30 tablets.

Manufactured by:

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Fukushima
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