

AUSTRALIAN PRODUCT INFORMATION

IRESSA® (GEFITINIB)

1 NAME OF THE MEDICINE

Gefitinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg of gefitinib.

Gefitinib is a white powder and a free base. It has pKas of 5.4 and 7.2 and therefore ionises progressively in solution as the pH falls. Gefitinib can be defined as sparingly soluble at pH 1, but is practically insoluble above pH 7, with the solubility dropping sharply between pH 4 and 6. Gefitinib is achiral.

Excipients with known effect: Each tablet contains lactose monohydrate. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Film-coated tablets (tablet).

The tablets are brown, round, biconvex, impressed with “IRESSA 250” on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) whose tumours express activating mutations of the EGFR tyrosine kinase.

4.2 Dose and method of 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.

Dosage adjustment

No dosage adjustment is required on the basis of patient age, body weight, gender, ethnicity, renal function or in patients with moderate to severe hepatic impairment due to liver metastases. Gefitinib exposure is increased in patients with moderate to severe hepatic impairment due to cirrhosis or hepatitis (see section 5.2 Pharmacokinetic properties). These patients should be closely monitored for adverse events.

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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

EGFR mutation assessment

When considering the use of IRESSA 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. Analytical performance characteristics with respect to tissue results (specificity, sensitivity, negative predictive value and positive predictive value) should be equivalent or better than that obtained with the Qiagen Therascreen EGFR RGQ PCR kit used in the IFUM study (see Section 5.1 Pharmacodynamic properties). 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 Section 5.1 Pharmacodynamic properties).

Interstitial Lung Disease

Interstitial Lung Disease (ILD), which may be acute in onset, has been observed in patients receiving IRESSA, and some cases have been fatal. Patients typically have an acute onset of dyspnoea associated with cough, low grade fever, respiratory distress and arterial oxygen desaturation. Symptoms may become severe within a short time. If patients present with worsening of respiratory symptoms such as dyspnoea, cough and fever, IRESSA should be interrupted and prompt investigation initiated. Radiological investigations frequently show pulmonary infiltrates or interstitial shadowing with ground glass appearance. If ILD is confirmed, IRESSA should be discontinued and the patient treated appropriately.

In the placebo-controlled ISEL trial (1692 patients), the incidence of ILD-type events in the overall population was similar and approximately 1% in both treatment arms. The majority of ILD-type event reports 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 was fatal, and this occurred in a patient receiving placebo.

In the INTEREST trial (1466 patients), the incidence of ILD was 1.4% in the IRESSA group and 1.1% in the docetaxel group. One ILD event was fatal and this occurred in a patient receiving IRESSA.

In the IPASS trial (1217 patients) in Asian patients, the incidence of ILD-type events was 2.6% on the IRESSA treatment arm versus 1.4% on the carboplatin/paclitaxel treatment arm.

In a Japanese Pharmacoepidemiological case control study (see Section 4.8 Adverse effects) 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 (\geq 65 years old), and extensive areas adherent to pleura (\geq 50%).

Cerebrovascular events

Cerebrovascular events have been reported in clinical studies of IRESSA. A relationship with IRESSA has not been established. An increased risk of cerebral haemorrhage in adult patients with NSCLC receiving IRESSA has not been established

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 the 45 patients enrolled. A further case of CNS haemorrhage in a child with an ependymoma from a trial with IRESSA alone has been reported.

Severe or persistent diarrhoea, nausea, vomiting or anorexia

Patients should be advised to seek medical advice promptly in the event of developing severe or persistent diarrhoea, nausea, vomiting or anorexia (see Section 4.8 Adverse effects). These symptoms should be managed as clinically indicated.

Eye symptoms

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.

Combination cytotoxic therapy

Randomised controlled trials have demonstrated that IRESSA combined with doublet, platinum-based cytotoxic chemotherapy in advanced NSCLC provides no added benefit over the cytotoxic chemotherapy alone. IRESSA should therefore only be used as monotherapy in advanced NSCLC in patients who have previously received treatment with cytotoxic chemotherapy.

Gastrointestinal perforation

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.

QT interval prolongation

Data from non-clinical (in vitro) studies indicate that gefitinib has the potential to inhibit the cardiac action potential repolarization process (e.g. QT interval). However, safety data obtained from clinical trials and post-marketing surveillance have not suggested any adverse cardiac effects of gefitinib.

Severe cutaneous reactions

Severe cutaneous reactions have been reported with gefitinib including erythema multiforme and life-threatening reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis (e.g. progressive skin rash often with blisters or mucosal lesions). Treatment with gefitinib should be interrupted if the patient develops severe bullous, blistering or exfoliative conditions, and discontinued if Stevens-Johnson syndrome or toxic epidermal necrolysis are confirmed.

Use in hepatic impairment

Liver function test abnormalities (including increases in alanine aminotransferase, aspartate aminotransferase, bilirubin) have been observed (see Section 4.8 Adverse effects) 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 changes in liver function. Discontinuation should be considered if changes are severe.

Use in renal impairment

There have been reports of renal failure secondary to dehydration due to diarrhoea, nausea, vomiting and/or anorexia, or associated with pre-renal factors such as concurrent infections or concomitant medications including chemotherapy. In more severe or persistent cases of diarrhoea, or cases leading to dehydration, particularly in patients with known risk factors (eg renal disease, concurrent vomiting, concomitant medications that impair ability to tolerate dehydration such as NSAIDs and diuretics), IRESSA therapy should be interrupted and appropriate measures taken to intensively rehydrate the patient. In addition, urea, electrolytes and creatinine should be monitored in patients at high risk of dehydration.

Paediatric use

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

Use in the elderly

No data available.

Effects on laboratory tests

Liver function test abnormalities (including increases in alanine aminotransferase, aspartate aminotransferase, bilirubin) have been observed (see Section 4.8 Adverse effects) uncommonly presenting as hepatitis. There have been isolated reports of hepatic failure which in some cases led to fatal outcomes.

4.5 Interactions with other medicines and other forms of interactions

In vitro studies with human hepatic microsomes have shown that the metabolism of IRESSA is mainly via the CYP3A4 isoform of the hepatic cytochrome P-450 system. IRESSA may be expected to interact with other drugs that induce, inhibit or are metabolised by this system. IRESSA showed little enzyme induction effect in animal studies and in vitro studies have shown that IRESSA has limited potential to inhibit CYP2D6.

The clinically or potentially significant clinical drug interactions between IRESSA and the following drugs/drug classes are described below.

Other drugs that affect IRESSA

Demonstrated interactions

Medicines that inhibit CYP3A4

Co-administration with itraconazole (a CYP3A4 inhibitor) resulted in an 80% increase in the mean AUC of IRESSA 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 IRESSA metabolism.

Medicines (e.g. ranitidine) that increase gastric pH

In a trial in healthy volunteers co-administration of ranitidine at a dose that caused sustained elevations in gastric pH, ≥ 5 , resulted in a reduced mean IRESSA AUC by 47%. As a consequence, drugs that cause significant sustained elevations in gastric pH may reduce plasma concentrations of IRESSA and therefore may reduce efficacy.

Rifampacin

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

Theoretical interactions

Other CYP3A4 inducers

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

Effects of IRESSA on other medicines

Demonstrated interactions

Medicines metabolised by CYP2D6

In a clinical trial in patients, IRESSA was co-administered with metoprolol (a CYP2D6 substrate). This resulted in a mean 35% increase in exposure to metoprolol. IRESSA may increase the blood concentrations of other co-administered drugs metabolised by CYP2D6.

Theoretical interactions

Warfarin

Although no formal drug interaction study has been conducted, elevations in Internationalised Normal Ratio (INR) and/or bleeding events have been reported in some patients taking warfarin. Consistent with standard anticoagulant therapy practice, patients taking warfarin should be monitored regularly for changes in prothrombin time or INR (see Section 4.8 Adverse effects).

Vinorelbine

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

Gefitinib given at 20 mg/kg/day (0.7-fold the clinical dose based on body surface area) for 4 weeks prior to mating until day 7 of gestation affected ovulation in female rats, resulting in a reduction in the number of corpora lutea.

Use in pregnancy – Category C

There are no data from the use of IRESSA in pregnant women. When gefitinib was administered during organogenesis, an increase in the incidence of incomplete ossifications was observed in rats and reduced foetal weights were observed in rabbits at maternally toxic doses. Malformations were not observed in rats; they were observed in rabbits only at a severely maternally toxic dose. Women of childbearing potential must be advised to avoid becoming pregnant while receiving IRESSA therapy.

Use in lactation

Mothers must be recommended to discontinue breast-feeding while receiving IRESSA therapy.

There are no data from the use of IRESSA in breast-feeding women. It is not known whether gefitinib or its metabolites are excreted in human milk. However, in lactating rats administered 5 mg/kg orally (about 0.2-fold the clinical dose based on body surface area), gefitinib and some metabolites were excreted in milk. When gefitinib was administered to the rat during gestation and lactation, there was a reduction in pup survival at a dose of 20 mg/kg/day (about 0.7-fold the clinical dose based on body surface area).

4.7 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.

4.8 Adverse effects (Undesirable effects)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at <http://www.tga.gov.au/reporting-problems>.

The most commonly reported adverse drug reactions (ADRs), occurring in more than 20% of the patients receiving IRESSA 250 mg, are diarrhoea, rash, pruritus, dry skin and acne. 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). However approximately 3% of patients stopped therapy due to an ADR.

In a phase II trial, Japanese patients experienced a higher frequency of ADRs compared to non-Japanese patients. Because of possible confounding factors in the two patient groups, it is uncertain if this difference is due to ethnic factors.

ADRs have been assigned to the frequency categories where possible based on the incidence of comparable Adverse Event reports in a pooled dataset from the IPASS, ISEL and INTEREST 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.

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 by system organ class and frequency

System Order Class	Frequency	Event
Metabolism and nutrition disorders	Very Common	Anorexia mild or moderate (CTC grade 1 or 2).
Eye disorders	Common	Keratitis, conjunctivitis, blepharitis, and dry eye*, mainly mild (CTC grade 1).
	Uncommon	Corneal erosion, reversible and sometimes in association with aberrant eyelash growth.
Vascular disorders	Common	Haemorrhage, such as epistaxis and haematuria.
Respiratory, thoracic and mediastinal disorders	Common	Interstitial lung disease, 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***, including angioedema and urticaria
	Uncommon	Palmar-plantar erythrodysesthesia syndrome

System Order Class	Frequency	Event
	Rare	Bullous conditions including toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, and cutaneous vasculitis****
Renal and urinary disorders	Common	Asymptomatic laboratory elevations in blood creatinine, proteinuria, cystitis
	Rare	Haemorrhagic cystitis****
General disorders	Very Common	Asthenia, predominantly mild (CTC grade 1).
	Common	Pyrexia

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

*This event can occur in association with other dry conditions (mainly skin reactions) seen with IRESSA.

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

***The overall incidence of adverse events of allergic reaction reported in the pooled analysis of the ISEL, INTEREST and IPASS Phase III trials was 1.1% (28/2462 patients).

****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 (Sep 2009), which assumes there were 3 reports across the monotherapy studies.

Postmarket experience

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

Severe cutaneous reactions have been reported with gefitinib including erythema multiforme and life-threatening reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis (e.g. progressive skin rash often with blisters or mucosal lesions).

4.9 Overdose

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

There is no specific treatment in the event of overdose of IRESSA. 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. Adverse reactions associated with overdose should be treated symptomatically; in particular severe diarrhoea should be managed as clinically indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Gefitinib is a selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, commonly expressed in solid human tumours of epithelial origin. Gefitinib has been demonstrated to inhibit the growth of a wide range of human tumour xenografts in nude mice, to inhibit angiogenesis in xenografts, and to increase apoptosis and inhibit invasiveness and secretion of angiogenic factors in human cancer cell lines *in vitro*. In animal or *in vitro* studies, gefitinib has

also been demonstrated to enhance the anti-tumour activity of chemotherapy, radiotherapy and hormonal therapy.

Resistance

Most NSCLC tumours with sensitizing EGFR kinase mutations eventually develop resistance to gefitinib treatment with a median time to disease progression of around 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 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.

Clinical trials

Phase III studies

IPASS

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] 0.74, 95% CI 0.65 to 0.85, p<0.0001), the primary endpoint of the trial. Patients were randomised to either IRESSA 250 mg once daily or carboplatin/paclitaxel AUC 5 or 6 mg/mL/min/200mg/m² iv every 3 weeks. The effect was not constant over time, initially favouring carboplatin/paclitaxel and then favouring gefitinib, potentially driven by differences in PFS outcomes by EGFR mutation status. EGFR mutation status was a strong predictive biomarker for the effect of gefitinib compared to carboplatin/paclitaxel. In subgroup analysis of PFS by EGFR mutation status, gefitinib was significantly better than carboplatin/paclitaxel in patients with mutation-positive tumours whereas carboplatin/paclitaxel was significantly better than gefitinib in patients with mutation-negative tumours (see Table 2)

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 (see Table 2). The analysis was confounded by treatment on progression. Approximately half the patients progressing on gefitinib were transferred to carboplatin/paclitaxel and approximately half the patients progressing on carboplatin/paclitaxel were transferred to an EGFR tyrosine kinase inhibitor.

Table 2 Efficacy outcomes for gefitinib versus carboplatin/paclitaxel from the IPASS study (ITT Population)

Population	N	PFS ^{abcd}	OS ^{acd}	ORR [95% CI] ^{ade}
Overall	1217 (609 vs 608)	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;	43.0 % vs 32.2 % [5.3, 16.1]
EGFR M+	261 (132 vs 129)	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	71.2 % vs 47.3 % [12.0, 34.9]

Population	N	PFS ^{abcd}	OS ^{acd}	ORR [95% CI] ^{ade}
EGFR M-	176 (91 vs 85)	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	1.1 % vs 23.5 % [-32.5, -13.3]
EGFR Mutation Unknown	780	HR 0.68 [0.58, 0.81] 6.6 m vs 5.8 m p<0.0001	HR 0.82 [0.70, 0.96] 18.9 m vs. 17.2 m	43.3 % vs 29.2 % [7.3%, 20.6%]

a Values presented are for gefitinib versus carboplatin/paclitaxel

b Results were similar in the per protocol analysis

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

d Patients were considered EGFR mutation positive (M+) if one of at least 29 EGFR mutations was detected by Amplification Refractory Mutation System (ARMS) using DxS EGFR 29 mutation detection kit. Patients were deemed EGFR mutation negative (M-) if samples were successfully analysed and none of the 29 EGFR mutations was detected

e Confidence Intervals (CI) presented are 95% CI for the difference in ORR

N - Number of patients randomised; HR - Hazard ratio (hazard ratios <1 favour IRESSA); PFS - Progression Free Survival; OS- Overall Survival; ORR - Objective Response Rate; CI - Confidence Interval

Quality of life outcomes differed according to EGFR mutation status. In EGFR mutation-positive patients, significantly more IRESSA-treated patients experienced an improvement in quality of life and lung cancer symptoms versus carboplatin/paclitaxel whereas the reverse was the case in EGFR mutation negative patients (see Table 3).

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

Population	N	FACT-L QoL ^{ab} improvement rate (%)	LCS symptom ^{ab} improvement rate (%)
Overall	1151 (590 vs 561)	48.0 % vs 40.8 % p=0.0148	51.5 % vs 48.5 % p=0.3037
EGFR M+	259 (131 vs 128)	70.2 % vs 44.5 % p<0.0001	75.6 % vs 53.9 % p=0.0003
EGFR M-	169 (89 vs 80)	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

b Evaluable for QoL analysis: subset of the ITT containing patients with an evaluable baseline QoL assessment and at least 1 evaluable post-baseline QoL assessment.

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

INTEREST

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 (58% of patients were refractory to previous chemotherapy), IRESSA was proven to be non-inferior to docetaxel (75 mg/m²) in terms of overall survival (Hazard Ratio [HR] 1.02, 96%CI [0.91 to 1.15])

CI entirely below non-inferiority limit of 1.154, median 7.6 vs 8.0 months), (see Table 4). Patients were randomised to IRESSA 250 mg once daily or docetaxel 75 mg/m² iv every 3 weeks.

Table 4 Efficacy outcomes for gefitinib versus docetaxel from the INTEREST study

Population	N ^d	OS ^{abce}	PFS ^{abce}	ORR [95 % CI] ^{abef}
Overall	1433 (723 vs 710)	HR 1.020 [0.905, 1.150] ^c 7.6 m vs 8.0 m p=0.7332	HR 1.04 [0.93,1.18] 2.2 m vs 2.7 m p=0.4658	9.1 % vs 7.6 % [-1.5 %, 4.5 %]
EGFR M+	44 (22 vs 22)	HR 0.83 [0.41, 1.67] 14.2 m vs 16.6 m p=0.6043	HR 0.16 [0.05, 0.49] 7.0 m vs 4.1 m p=0.0012	42.1 % vs 21.1 % [-8.2 %, 46.0 %]
EGFR M-	253 (119 vs 134)	HR 1.02 [0.78, 1.33] 6.4 m vs 6.0 m p=0.9131	HR 1.24 [0.94,1.64] 1.7 m vs 2.6 m p=0.1353	6.6 % vs 9.8 % [-10.5 %, 4.4 %]

- a Values presented are for IRESSA versus docetaxel.
b Results seen in the intention to treat analysis (for overall) were similar
c “m” is medians in months. Numbers in square brackets are 96 % confidence interval for overall survival HR in the overall population, or otherwise 95 % confidence intervals for HR
d Per-protocol analysis for Overall and Intention to treat for EGFR mutation positive and negative
e Evaluable for response: subset of the per-protocol with uni-dimensional measurable disease per the RECIST criteria
f Confidence Intervals (CI) presented are 95% CI for the difference in ORR

NR Not reached; N Number of patients randomised; HR Hazard ratio (hazard ratios <1 favour IRESSA); PFS Progression Free Survival; OS Overall Survival; ORR Objective Response Rate; CI Confidence Interval

The co-primary analysis evaluating the 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 1.09, 95% CI 0.78 to 1.51, p=0.6199, median 8.4 vs 7.5 months).

ISEL

The ISEL study was a phase III randomised, double blind, parallel group clinical trial comparing IRESSA 250 mg once daily plus BSC versus placebo plus BSC in 1692 pre-treated patients with locally advanced or metastatic NSCLC who had received 1 or 2 prior chemotherapy regimens and were refractory (90%) or intolerant to their most recent regimen (see Table 5).

Table 5 Efficacy outcomes for IRESSA versus placebo from the ISEL study

Population	N	OS ^{abce}	Time to treatment failure ^{abce} [95% CI]	ORR ^{adf}
Overall	1692 (1129 vs 563)	HR 0.89 [0.77,1.02] 5.6 m vs 5.1 m p=0.0871	HR 0.82 [0.73, 0.92] 3.0 m vs 2.6 m p=0.0006	8.0 % vs 1.3 % [4.7 %, 8.8 %]
EGFR M+	26 (21 vs 5)	HR NC NR vs 4.3 m	HR 0.79 [0.20, 3.12] 10.8 m vs 3.8m ns	37.5 % vs 0 % [-15.1 %, 61.4 %]

Population	N	OS ^{abce}	Time to treatment failure ^{abce} [95% CI]	ORR ^{adf}
EGFR M-	189 (132 vs 57)	HR 1.16 [0.79, 1.72] 3.7 m vs 5.9 m ns	HR 1.10 [0.78, 1.56] 2.0 m vs 2.6 m ns	2.6 % vs 0 % [-5.6 %, 7.3 %]

a Values presented are for IRESSA versus placebo.

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

c Stratified log rank test for overall; otherwise cox proportional hazards model

d Evaluable for response: subset of the per-protocol with uni-dimensional measurable disease per the RECIST criteria

e Intention to treat analysis

f Confidence Intervals (CI) presented are 95% CI for the difference in ORR

N Number of patients randomised; NC Not calculated for overall survival HR as the number of events is too few; NR Not reached; HR Hazard ratio (hazard ratios <1 favour IRESSA); NS – not significant

Exploratory analysis of EGFR biomarkers was statistically inconclusive however response rates in ISEL were higher among IRESSA treated patients with EGFR mutation-positive tumours.

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; see Section 4.4 Special warnings and precautions for use). 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% relative to the matched tissue results using the same Qiagen Therascreen kit. The positive and negative predictive values of ctDNA were 98.6% and 93.8%, respectively (Table 6). Objective response rate in the IFUM full analysis set population was 69.8% (95% CI: 60.5% to 77.7%). The ORR in those patients within the full analysis set population who were ctDNA mutation positive was 77.3% (95% CI: 65.8 to 85.7).

Table 6 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
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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

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 a 2 to 8-fold accumulation with steady state exposure achieved after 7 to 10 doses. At steady state, the ratios of C_{max} to C_{min} 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.

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 (see Section 4.5 Interactions with other medicines and other forms of interactions).

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.

The major metabolite identified in human plasma is O-desmethyl gefitinib. It was 14-fold less potent than gefitinib at inhibiting EGFR stimulated cell growth and it is therefore unlikely that it contributes significantly 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.

Excretion

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

Population kinetics

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.

Hepatic insufficiency

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 pharmacokinetic study in 31 patients with solid tumours and normal (14 patients), moderate (13 patients) or severe (4 patients) hepatic dysfunction due to liver metastases. It was shown that following daily dosing of 250 mg IRESSA for 28 days, 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 the 4 patients with severe hepatic dysfunction due to liver metastases suggested that steady state exposures in these patients are also similar to those with normal hepatic function.

Other populations

Patients that have never smoked, have adenocarcinoma histology, are female gender or are of Asian ethnicity, are associated with a higher rate of EGFR mutation positive tumours

5.3 Preclinical safety data

Genotoxicity

There was no evidence for a genotoxic potential of gefitinib in assays for gene mutation (bacteria and mammalian cells *in vitro*) and clastogenicity (mammalian cells *in vitro* and *in vivo* rat micronucleus test).

Carcinogenicity

A 2-year oral (gavage) carcinogenicity study in rats resulted in a small but statistically significant increase in the incidence of hepatocellular adenomas in both male and female rats and mesenteric lymph node haemangiosarcomas in female rats at the high dose of 10 mg/kg/day. An increased incidence of hepatocellular adenomas was also seen in a 2-year oral (gavage) carcinogenicity study in mice dosed at 50 mg/kg/day and above. The dose of 10 mg/kg/day in rats and 50 mg/kg/day in mice was associated with systemic exposure (based on plasma AUC) of approximately two (2) and three (3) times that anticipated in patients at the recommended clinical dose. The non-effect-dose-level (NOEL) for these effects was 5 mg/kg/day in rats and 10 mg/kg/day in mice, which was associated with systemic exposure of approximately 1.2 and 0.3 times the anticipated value in patients at the recommended clinical dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets contain the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, hypromellose, macrogol 300, titanium dioxide, iron oxide yellow CI77492 and iron oxide red CI77491.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

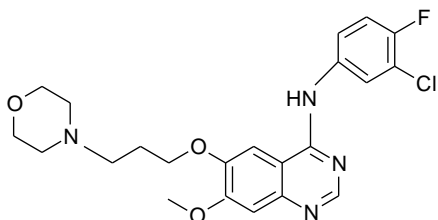
IRESSA is available in packs of 30 tablets in PVC/aluminium blisters.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure



Chemical name: N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine.

Molecular formula: C₂₂H₂₄ClFN₄O₃

Molecular weight: 446.90

CAS number

184475-35-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

28 April 2003

10 DATE OF REVISION

13 January 2021

Summary table of changes

Section changed	Summary of new information
4.2	PI correction to reinstate tablet dispersal in water paragraph.
4.4 and 4.8	Addition of Severe cutaneous reactions as per TGA request 29 Nov 2019 (TRIM ref: D19-6458963; PSAB issue: 10206)
4.8	Addition of Palmar-plantar erythrodysesthesia syndrome (CDS 31 August 2020)

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