PRODUCT MONOGRAPH

[Pr]NAT-Gefitinib

Gefitinib Tablets

250 mg

Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	All Nonmedicinal Ingredients
Oral	Tablet, 250 mg gefitinib	lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone K-30, sodium lauryl sulfate, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, yellow iron oxide, red iron oxide

INDICATIONS AND CLINICAL USE

NAT-Gefitinib (gefitinib) is indicated for the first line treatment of patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have activating mutations of the EGFR-TK (see WARNINGS AND PRECAUTIONS—Monitoring and Laboratory Tests).

This indication was based on progression-free survival (PFS). After 78% of trial patients had died, no statistically significant difference in overall survival (OS) was demonstrated with first line gefitinib compared to the first line chemotherapy doublet in patients with EGFR mutation positive tumours in the IPASS study (see CLINICAL TRIALS).

Geriatrics (≥ 65 years of age):
No differences in safety or efficacy were observed between younger and older patients (see WARNINGS AND PRECAUTIONS—Special Populations).

Paediatrics (≤ 16 years of age):
NAT-Gefitinib is not indicated for use in paediatric patients, as safety and effectiveness have not been established (see WARNINGS AND PRECAUTIONS – Special Populations).

CONTRAINDICATIONS

Patients who are hypersensitive to gefitinib or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- NAT-Gefitinib (gefitinib) should be administered under the supervision of a qualified health professional who is experienced in the treatment and management of patients with cancer.
- NAT-Gefitinib should not be used in patients with EGFR mutation negative tumours (see WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests; CLINICAL TRIALS).
- NAT-Gefitinib has not been studied in patients with severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions).
- Isolated cases of hepatic failure and fulminant hepatitis, including fatalities, have been reported with gefitinib use (see WARNINGS AND PRECAUTIONS – Hepatotoxicity).
- Gastrointestinal perforation (including cases with a fatal outcome) was observed in patients treated with gefitinib (see WARNINGS AND PRECAUTIONS – Gastrointestinal)

Effects on Ability to Drive and Use Machinery

NAT-Gefitinib is not expected to impair a patient's ability to drive or use machines. However, some patients may occasionally feel weak. If this happens, patients should not drive or operate machinery.

Cardiac

No thorough QT/QTc study was performed to rule out the effect of gefitinib on QT prolongation. Routine ECG assessments during clinical trials did not identify any concerns regarding QT prolongation (see DETAILED PHARMACOLOGY – Pharmacodynamics).

Carcinogenicity

Pre-clinical studies have identified a statistically significant increase in hepatocellular adenomas in rats and mice and in mesenteric lymph node hemangiosarcomas in rats. The clinical relevance of these findings is unknown (see TOXICOLOGY –Carcinogenicity & Mutagenicity).

Drug Interactions

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

CYP3A4: Gefitinib is primarily metabolized by CYP3A4.

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 potentially reduce efficacy (see DRUG INTERACTIONS).

Substances that are inhibitors of CYP3A4 activity (e.g. ketoconazole, macrolides, grapefruit juice) may decrease metabolism and increase gefitinib plasma concentrations. This may be clinically relevant and caution is advised as adverse experiences are related to dose and exposure (see DRUG INTERACTIONS).

CYP2D6: In vitro studies demonstrate gefitinib has potential to inhibit CYP2D6. In a clinical trial in cancer patients, gefitinib was co-administered with metoprolol (a CYP2D6 substrate). This resulted in a 35% increase in metoprolol exposure. Such an increase might potentially be relevant for CYP2D6 substrates with narrow therapeutic index. When the use of CYP2D6 substrates are considered in combination with gefitinib, a dose modification of the CYP2D6 substrate should be considered, especially for products with a narrow therapeutic window (see DRUG INTERACTIONS).

Gastrointestinal

Diarrhea, Dehydration and Renal Dysfunction: Gefitinib use is very commonly associated with diarrhea, nausea, vomiting, stomatitis, and anorexia. Patients should be advised to seek medical advice promptly in the event of developing severe or persistent diarrhea, nausea, vomiting or anorexia. These symptoms should be managed as clinically indicated as any subsequent dehydration may lead to renal dysfunction if left untreated (see DOSAGE AND ADMINISTRATION – Recommended Dose and Dose Adjustment).

Gastrointestinal perforation: Gastrointestinal (GI) perforation has been reported uncommonly (0.2%) in patients taking gefitinib, and some cases have been fatal. 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, bowel metastases at sites of perforation, diverticulitis, GI obstructions, or advanced bowel disease. If a diagnosis of GI perforation is confirmed, treatment with NAT-Gefitinib should be interrupted or discontinued.

Haematologic

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

Two Phase II trials using the combination gefitinib/vinorelbine have been discontinued due to a high incidence of CTC grade 3 and 4 neutropenia. When used in combination, gefitinib aggravated the neutropenic effect of vinorelbine.

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

Haemorrhage

Throughout the gefitinib lung cancer clinical trials, the incidence of haemoptysis/pulmonary haemorrhage reported on the gefitinib arm has consistently been higher than that reported on the comparator arm (e.g. on IPASS 3.5% vs. 3.1%, gefitinib vs. carboplatin/paclitaxel. Pooled incidence: gefitinib 5.3% vs. placebo 4.4%; gefitinib 5.0% vs. docetaxel 3.5%; gefitinib 3.7% vs. other chemotherapy 2.8%; overall pooled gefitinib incidence: 4.8%). This may in part be explained by the longer duration of treatment on the gefitinib arm.

Epistaxis and haematuria are commonly associated with gefitinib therapy (4.3%).

Hepatic/Biliary/Pancreatic

Hepatotoxicity: Liver function test abnormalities (including increases in alanine aminotransferase, aspartate aminotransferase, bilirubin) have been observed, uncommonly presenting as hepatitis. Isolated cases of hepatic failure and fulminant hepatitis, including fatalities, have been reported with gefitinib use. Therefore, periodic liver function testing is recommended. NAT-Gefitinib should be used cautiously in the presence of mild to moderate changes in liver function. Discontinuation should be considered if changes are severe.

Ophthalmologic

Conjunctivitis, blepharitis, and dry eye are commonly seen in patients treated with gefitinib (6.7%) and are generally mild in nature (CTC grade 1). Corneal erosion occurs uncommonly (0.3%), is reversible and sometimes is associated with aberrant eyelash growth. The safety of wearing contact lenses during gefitinib therapy has not been adequately studied.

Patients should be advised to seek medical advice promptly in the event of developing any 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 (see ADVERSE REACTIONS). If a diagnosis of ulcerative keratitis is confirmed, treatment with NAT-Gefitinib should be interrupted, and if symptoms do not resolve, or recur on reintroduction of gefitinib, permanent discontinuation should be considered.

Cases of corneal erosion have been reported during use of gefitinib. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with gefitinib treatment. Recent corneal surgery and contact lens wearing are known to be independent risk factors for ocular toxicity including corneal erosion.

These symptoms should be managed as clinically indicated (see DOSAGE AND ADMINISTRATION – Recommended Dose and Dosage Adjustment).

Renal

There have been reports of renal failure secondary to dehydration due to diarrhea, 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 diarrhea, or cases leading to dehydration, particularly in patients with known risk factors (e.g. renal disease, concurrent vomiting, concomitant medications that impair ability to tolerate dehydration such as NSAIDs and diuretics), NAT-Gefitinib therapy should be interrupted and appropriate measures taken to intensively rehydrate the patient.

In addition, urea, creatinine and electrolytes should be monitored in patients at high risk of dehydration.

Respiratory

Interstitial Lung Disease (ILD), which may be acute in onset, has been observed in patients receiving gefitinib at an overall incidence of about 1%, and approximately 1/3 of the cases have been fatal (See ADVERSE REACTIONS – Interstitial Lung Disease).

If patients present with worsening of respiratory symptoms such as dyspnoea, cough and fever, NAT-Gefitinib should be interrupted and prompt investigation initiated. If ILD is confirmed, NAT-Gefitinib should be discontinued and the patient treated appropriately.

The incidence of ILD-type events was 5.8% in patients receiving gefitinib in a post-marketing surveillance study in Japan (3350 patients) (see ADVERSE REACTIONS – Interstitial Lung Disease). In a Japanese Pharmacoepidemiological case-control study (see ADVERSE REACTIONS - Interstitial Lung Disease) in 3159 patients with NSCLC who were followed up for 12 weeks when receiving gefitinib or chemotherapy, the 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. The adjusted odds ratio (OR) of developing ILD was 3.2 (95% confidence interval (CI) 1.9 to 5.4) for gefitinib versus chemotherapy. This trial identified the following risk factors for developing ILD (irrespective of whether the patient received gefitinib or chemotherapy): 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%).

Skin

Rash is very common with gefitinib use (57.9%), mainly mild to moderate (CTC grade 1 or 2). Toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme occur rarely (0.04%), and some cases have been fatal (see DOSAGE AND ADMINISTRATION – Recommended Dose and Dosage Adjustment). Cutaneous vasculitis, skin fissures (including rhagades) have been reported. Preclinical work in guinea pigs indicates that gefitinib may be a potential skin (contact) sensitiser. Results of an in vitro phototoxicity study demonstrated that gefitinib may have phototoxicity potential.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women using gefitinib. Women of childbearing potential must be advised to avoid becoming pregnant. If gefitinib is used during pregnancy or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy. NAT-Gefitinib tablets may cause fetal harm when administered to a pregnant woman (See Part II, TOXICOLOGY - Reproduction & Teratology).

Nursing Women: It is not known whether gefitinib is excreted in human milk, however this is documented to occur in pre-clinical testing (See Part II, TOXICOLOGY - Reproduction and Teratology). Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breast-feeding while receiving NAT-Gefitinib therapy.

Paediatrics (≤ 16 years of age): 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 have been reported in 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. NAT-Gefitinib is not indicated for use in paediatric patients, as safety and effectiveness have not been established.

Geriatrics (≥ 65 years of age): Of the total number of patients participating in the INTEREST and ISEL trials, 37% were aged 65 or older. No differences in gefitinib safety or efficacy effect relative to the comparator were observed between younger and older patients.

Hepatic Impairment: Patients with moderate to severe hepatic impairment (Child Pugh B or C) due to cirrhosis have increased plasma concentrations of gefitinib (see ACTION AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). An average 3.1-fold increase in exposure to gefitinib in patients with moderate and severe hepatic impairment was observed in a phase I hepatic impairment study. 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.

In the pivotal trial IPASS, patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 2.5 times upper limit of normal (ULN) with no demonstrable liver metastases or greater than 5 times ULN in the presence of liver metastases were excluded due to potential hepatic concerns associated with the carboplatin/paclitaxel doublet. Consequently, the IPASS study does not contribute any data in this patient population.

CYP2D6 Poor Metabolisers: In a clinical trial of healthy volunteers, CYP2D6 poor metabolisers achieved a 2-fold higher mean exposure to gefitinib than in extensive metabolisers. The higher average gefitinib exposures achieved by individuals with no active CYP2D6 may be clinically relevant since adverse experiences are related to dose and exposure.

Monitoring and Laboratory Tests

Assessment of EGFR Mutation Status: EGFR mutation status must be known prior to starting NAT-Gefitinib therapy because only patients with an activating mutation of EGFR TK should be treated with NAT-Gefitinib (see INDICATION AND CLINICAL USE; CLINICAL TRIALS). When assessing the EGFR mutation status of a patient, it is important that a well-validated and robust methodology is chosen to minimize the possibility of false negative or false positive determinations.

Clinical characteristics of never smoker, adenocarcinoma histology, and female gender have been shown to be independent predictors of positive EGFR mutation status for both non-Asian and Asian patients. Asian patients also have a higher incidence of EGFR mutation positive tumours (approximately 40% positive rate) than non-Asian patients (approximately 10% positive rate). These clinical characteristics should not be used to guide treatment choice, however they may be helpful in guiding mutation testing. A patient must be defined as EGFR mutation positive before starting NAT-Gefitinib therapy.

Hematology and Chemistry Assessment: Electrolytes, BUN, creatinine, liver function tests (alanine aminotransferase, aspartate aminotransferase, bilirubin) should be performed at baseline and periodically during NAT-Gefitinib therapy.

Patients taking warfarin should be monitored regularly for changes in Prothrombin Time (PT) or INR (see DRUG INTERACTIONS).

Other

NAT-Gefitinib contains lactose. This should be considered when assessing the benefit: risk ratio of NAT-Gefitinib use in patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse drug reactions (ADR) found to be associated with treatment with gefitinib are shown in Table 1. The most common adverse drug reactions reported at the recommended 250 mg daily dose, occurring in more than 20% of patients, are diarrhoea, sometimes associated with dehydration and mainly mild or moderate in nature (CTC grade 1 or 2) and less commonly, severe (CTC grade 3 or 4); and skin reactions (including rash, acne, dry skin and pruritus) (Table 1). 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. The onsets of these ADRs usually occurred within the first month of therapy and were generally mild and non-cumulative as well as reversible.

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) (see Part II, CLINICAL TRIALS). 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. The 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.

Table 1 Adverse Drug Reactions by frequency and system/organ (pooled safety data from ISEL, INTEREST and IPASS phase III clinical trials)

Very common (≥10%)	
Gastrointestinal disorders:	• Diarrhoea (34.9%), mainly mild or moderate in nature (CTC grade 1 or 2) and, less commonly, severe (CTC grade 3 or 4). • Nausea (17.8%), mainly mild in nature (CTC grade 1). • Vomiting (13.8%), mainly mild or moderate in nature (CTC grade 1 or 2). • Stomatitis (11.0%), predominantly mild in nature (CTC grade 1)
Hepatobiliary disorders:	• Elevations in alanine aminotransferase (11.4%), mainly mild to moderate.
Metabolism and nutrition disorders:	• Anorexia (19.7%), mild or moderate in nature (CTC grade 1 or 2).
Skin and subcutaneous tissue disorders:	• Skin reactions (57.9%), mainly a mild or moderate (CTC grade 1 or 2) pustular rash, sometimes itchy with dry skin, including skin fissures on an erythematous base
General Disorders and administration site conditions:	• Asthenia (17.7%), predominantly mild in nature (CTC grade 1)
Common (≥1 - <10%)	
Gastrointestinal disorders:	• Dehydration (1.8%), secondary to diarrhoea, nausea, vomiting or anorexia • Dry mouth* (2.0%), predominantly mild in nature (CTC grade 1)
Vascular disorders:	• Haemorrhage (4.3%), such as epistaxis and haematuria
Hepatobiliary disorders:	• Elevations in Aspartate aminotransferase (7.9%), mainly mild to moderate • Elevations in total bilirubin (2.7%), mainly mild to moderate
Renal and urinary disorders:	• Asymptomatic laboratory elevations in blood creatinine (1.5%) • Proteinuria (7.7%) • Cystitis (1.1%)
Skin and subcutaneous tissue disorders:	• Nail disorder (7.9%) • Alopecia (4.7%)
General disorders and administration site conditions:	• Pyrexia (8.7%)

Eye disorders:	• Conjunctivitis, blepharitis, and dry eye*(6.7%), mainly mild in nature (CTC grade 1).
Respiratory, thoracic and mediastinal disorders:	• Interstitial lung disease (1.3%), often severe (CTC grade 3-4). Fatal outcomes have been reported.
Uncommon (≥0.1 - <1%)	
Gastrointestinal disorders:	• Pancreatitis (0.1%) • Gastrointestinal perforation (0.2%)
Hepatobiliary disorders	• Hepatitis*** (0.2%)
Eye disorders:	• Keratitis (0.1%), Corneal erosion (0.3%), reversible and sometimes in association with aberrant eyelash growth
Skin and subcutaneous tissue disorders:	• Allergic reactions** (0.9%), including angioedema and urticaria.
Rare (≥0.01 - <0.1%)	
Skin and subcutaneous tissue disorder:	• Bullous conditions including, toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme (0.04%). • Cutaneous vasculitis****
Renal and urinary disorders	• Hemorrhagic cystitis****

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

** The overall incidence of AEs of allergic reaction reported in the pooled analysis of the ISEL, INTEREST and IPASS trials was 1.5% (36 patients). Fourteen of the 36 patients were excluded from the reported frequency as their reports contained evidence of either a non-allergic aetiology or that the allergic reaction was the result of treatment with another medication.

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

Clinical Trial Adverse Drug Reactions

IPASS STUDY (D791A00007)

In IPASS, the most commonly reported adverse events for patients treated with gefitinib were diarrhoea and skin reactions (including rashes/acnes, dry skin and pruritus). Overall, for gefitinib-treated patients with an EGFR mutation positive status, the profile of the most common adverse events was similar to that reported in the overall population and consistent with the known safety profile of gefitinib.

Gefitinib had a more favourable tolerability profile than carboplatin / paclitaxel doublet chemotherapy, indicated by fewer CTC grade 3, 4 or 5 adverse events (31.6% versus 62.5%), fewer dose modifications due to toxicity (16.1% versus 35.2% [carboplatin]/37.5% [paclitaxel]) and fewer adverse events leading to discontinuation of randomized treatment (6.9% versus 13.6%). In addition, fewer treatment-related adverse events (88.6% versus 96.6%) were reported with gefitinib compared with carboplatin / paclitaxel.

Table 2 summarizes the most commonly reported adverse events observed with gefitinib and carboplatin/paclitaxel therapies in the IPASS trial irrespective of causality.

Table 2 Most common adverse events (those occurring in at least 10% of patients in either treatment group) or adverse events with a difference in incidence of >5% between treatment groups (IPASS; EFS population)

System organ class and preferred term	Number (%) of patients[a]	
	Gefitinib 250 mg (N=607) Overall[b]	Carboplatin/ Paclitaxel (N=589) Overall[b]
Blood and lymphatic disorders[c]		
Anaemia	43 (7.1)	150 (25.5)
Neutropenia	15 (2.5)	223 (37.9)
Leukopenia	13 (2.1)	146 (24.8)
Thrombocytopenia	8 (1.3)	71 (12.1)
Gastrointestinal disorders		
Diarrhoea	283 (46.6)	128 (21.7)
Nausea	101 (16.6)	261 (44.3)
Stomatitis	81 (13.3)	42 (7.1)
Vomiting	78 (12.9)	196 (33.3)
Constipation	73 (12.0)	173 (29.4)
General disorders and administration site conditions		
Fatigue	87 (14.3)	219 (37.2)
Pyrexia	54 (8.9)	61 (10.4)
Infections and Infestations		
Paronychia	82 (13.5)	0 0
Investigations		
ALT increased	64 (10.5)	31 (5.3)
AST increased	53 (8.7)	19 (3.2)
White blood cell count decreased	5 (0.8)	52 (8.8)
Neutrophil count decreased	0 0	40 (6.8)
Metabolism and Nutrition disorders		
Anorexia	117 (19.3)	235 (39.9)
Musculoskeletal and connective tissue disorders		
Myalgia	47 (7.7)	186 (31.6)
Arthralgia	39 (6.4)	113 (19.2)
Nervous system disorders		
Peripheral sensory neuropathy	23 (3.8)	141 (23.9)
Hypoaesthesia	21 (3.5)	154 (26.1)
Neuropathy peripheral	9 (1.5)	97 (16.5)
Psychiatric disorders		
Insomnia	88 (14.5)	108 (18.3)
Respiratory, thoracic and mediastinal disorders		
Cough	57 (9.4)	62 (10.5)
Skin and subcutaneous tissue disorders		
Rash	313 (51.6)	120 (20.4)
Dry skin	145 (23.9)	17 (2.9)

System organ class and preferred term	Number (%) of patients[a]	
	Gefitinib 250 mg (N=607) Overall[b]	Carboplatin/ Paclitaxel (N=589) Overall[b]
Pruritus	107 (17.6)	71 (12.1)
Alopecia	67 (11.0)	344 (58.4)
Acne	66 (10.9)	4 (0.7)
Dermatitis acneiform	35 (5.8)	2 (0.3)

[a] Percentages are of total patients in each treatment group presented by decreasing order of incidence in the gefitinib group within the System Organ Class. Patients are counted once within any preferred term.

[b] Overall includes all adverse events that occurred whilst receiving first-line treatment or within 28 days after discontinuation.

[c] Clinically significant laboratory findings were only reported as adverse events if a criterion for a serious adverse event was fulfilled: the abnormality caused study treatment to be discontinued, or the investigator insisted the abnormality was to be reported as an adverse event. Therefore, laboratory findings worsening from baseline to CTC grade 3 or 4 should be referred to for the primary assessment of haematological and liver function toxicity. ALT: alanine aminotransferase; AST: aspartate aminotransferase; EFS: Evaluable-for-safety; N: Number of patients

Formal statistical analyses were performed for ten pre-specified events possibly associated with gefitinib or carboplatin/paclitaxel treatment. This included relevant adverse events of any CTC grade and laboratory parameter values of CTC grade $\geq$ 3 (worsenings from baseline only) occurring during the period on randomized treatment (Table 3). Events of rashes/acnes, diarrhoea and CTC Grade $\geq$ 3 liver transaminases were reported at a statistically significantly higher incidence in the gefitinib arm. Events of neurotoxicity, and CTC Grade $\geq$ 3 haematological toxicity (CTC Grade $\geq$ 3 neutropenia, leukopenia, thrombocytopenia, and anaemia) were reported at a statistically significantly higher incidence in the carboplatin/paclitaxel arm. Although nausea and vomiting were included in the group of five events considered possibly associated with gefitinib treatment, the incidence of both was statistically significantly higher in the carboplatin/paclitaxel arm despite premedication.

Table 3 Analysis of specific safety events (IPASS; EFS population)

Event [a]	Gefitinib 250 mg (N=607)		Carboplatin/Paclitaxel (N=589)		Adjusted p-value[b]
	n	(%)	n	(%)	
Events possibly associated with gefitinib					
Rashes/Acnes	398	(65.6)	132	(22.4)	<0.0001
Diarrhoea	274	(45.1)	128	(21.7)	<0.0001
Nausea	74	(12.2)	260	(44.1)	<0.0001
Vomiting	59	(9.7)	193	(32.8)	<0.0001
Elevated liver transaminases (CTC $\geq$3)[c]	57	(9.4)	6	(1.0)	<0.0001
Events possibly associated with carboplatin/paclitaxel					
Neurotoxicity	30	(4.9)	411	(69.8)	<0.0001
Neutropenia (CTC $\geq$ 3)[c]	4	(0.7)	385	(65.4)	<0.0001
Leukopenia (CTC $\geq$ 3)[c]	1	(0.2)	202	(34.3)	<0.0001
Anaemia (CTC $\geq$ 3)[c]	11	(1.8)	56	(9.5)	<0.0001
Thrombocytopenia (CTC $\geq$ 3)[c]	5	(0.8)	29	(4.9)	0.0001

[a] Data are derived from adverse events occurring on-treatment and during the 28 day follow-up period, and from laboratory data reported on-treatment. Percentages are of total patients in each treatment group presented in decreasing order of incidence in the gefitinib group for events possibly associated with gefitinib, and in decreasing order of incidence in the carboplatin/paclitaxel group for events possibly associated with carboplatin/paclitaxel.
[b] Calculated using the method of Westfall and Young 1993.
c Identified from the laboratory data, as abnormal laboratory results were not to be routinely reported as adverse events.
CTC: Common Terminology Criteria; EFS: Evaluable-for-safety; N: Number of patients

Interstitial Lung Disease (ILD)

In the phase III open-label IPASS trial (see Part II, CLINICAL TRIALS) 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.

In the INTEREST trial, the incidence of ILD type events was similar for both treatments (gefitinib 10 patients [1.4%] versus docetaxel 8 patients [1.1%]).

In the ISEL trial, 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 WARNINGS AND PRECAUTIONS - Respiratory) 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).

Post-Market Adverse Drug Reactions

The following safety signals have been raised from post-marketing adverse event reports: ILD, pancreatitis, allergic reactions (including angioedema and urticaria), hepatitis and pyrexia.

DRUG INTERACTIONS

Overview

Gefitinib showed no enzyme induction effects in animal studies. Human liver microsome studies demonstrated that *in vitro* gefitinib was not a potent inhibitor of any human CYP enzyme activities. At the highest concentration studied, it produced approximately 50% inhibition of

CYP2D6. In a clinical trial in cancer 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. However, such an increase has potential clinical relevance for CYP2D6 substrates with a narrow therapeutic index and caution is advised when co-administered with NAT-Gefitinib.

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. 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 potentially reduce efficacy.

Co-administration with itraconazole (a potent CYP3A4 inhibitor) resulted in an 80% increase in the mean AUC of gefitinib in healthy volunteers. Substances that are inhibitors of CYP3A4 activity (e.g., azole antifungals such as ketoconazole and itraconazole, macrolide antibiotics such as erythromycin and clarithromycin, protease inhibitors, grapefruit juice etc.) may decrease metabolism and increase gefitinib plasma concentrations. This increase may be clinically relevant as adverse experiences are related to dose and exposure. Therefore, caution should be used when administering CYP3A4 inhibitors with NAT-Gefitinib.

Co-administration of ranitidine (gastric pH above 5) reduced by 47% the mean gefitinib AUC in healthy volunteers. Drugs that cause significant sustained elevation in gastric pH (histamine H2-receptor antagonists such as ranitidine or cimetidine; proton-pump inhibitors) may reduce plasma concentrations of gefitinib and therefore potentially may reduce efficacy (see ACTION AND CLINICAL PHARMACOLOGY - Metabolism).

International Normalized Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin while on gefitinib therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

Drug-Drug Interactions

Table 4 Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
Metoprolol	↑ metoprolol exposure by 35%	Observation made in cancer patients.
Rifampicin	↓ mean AUC of gefitinib by 83%	Observation made in healthy volunteers.
Itraconazole	↑ mean AUC of gefitinib by 80%	Observation made in healthy volunteers.

Ranitidine	↓ mean AUC of gefitinib by 47%	Observation made in healthy volunteers using supratherapeutic doses.

Drug-Food Interactions

Grapefruit juice and other inhibitors of CYP3A4 may decrease metabolism and increase gefitinib plasma concentrations.

Drug-Herb Interactions

St. John's Wort and other inducers of CYP3A4 may potentially reduce the efficacy of gefitinib.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended daily dose of NAT-Gefitinib (gefitinib) is one 250 mg tablet with or without food. Higher doses do not produce a better response and lead to increased toxicity.

Dosage Adjustment

No dosage adjustment is required on the basis of patient age, body weight, gender, ethnicity or renal function. However, data are limited in patients with severe renal impairment (creatinine clearance ≤ 20 ml/min (see ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions) and caution is advised in these patients.

For patients unable to tolerate treatment after a therapy interruption for toxicity, NAT-Gefitinib should be discontinued and another treatment option should be considered.

Dosage Adjustment due to Toxicity

Poorly tolerated diarrhoea: Patients with poorly tolerated diarrhoea (sometimes associated with dehydration) may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg daily dose once toxicity has resolved.

Skin adverse drug reactions: Patients with 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 daily dose once toxicity has resolved.

Eye symptoms: Patients who develop eye symptoms should be evaluated and managed, including interruption of therapy with NAT-Gefitinib. Reinstatement of the 250 mg/day NAT-Gefitinib dose should be considered when symptoms and eye changes have resolved.

Respiratory symptoms: If patients present with acute onset or worsening of respiratory symptoms such as dyspnoea, cough and fever, NAT-Gefitinib should be interrupted and prompt

investigation initiated. If Interstitial Lung Disease (ILD) is confirmed, NAT-Gefitinib should be discontinued and the patient treated appropriately (see WARNINGS AND PRECAUTIONS - Respiratory and ADVERSE REACTIONS).

Hepatic Impairment: An average 3.1-fold increase in exposure to gefitinib in patients with moderate and severe hepatic impairment due to cirrhosis was observed in a phase I hepatic impairment study (see WARNINGS AND PRECAUTIONS – Special Populations and ACTION AND CLINICAL PHARMACOLOGY sections). This increase in exposure may be of clinical relevance since adverse experiences are related to dose and exposure to gefitinib. No dose adjustments are recommended for patients with moderate to severe hepatic impairment (Child Pugh B or C) however, these patients should be closely monitored. No dose adjustments are recommended for patients with elevated aspartate transaminase (AST), alkaline phosphatase or bilirubin due to liver metastases. These patients should be closely monitored for adverse events.

In patients with impaired liver function secondary to liver metastases, gefitinib exposure was similar for patients with moderate hepatic dysfunction compared to normal hepatic function. Data from four 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.

In the pivotal trial IPASS, patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 2.5 times upper limit of normal (ULN) with no demonstrable liver metastases or greater than 5 times ULN in the presence of liver metastases were excluded due to potential hepatic concerns associated with the carboplatin/paclitaxel doublet. Consequently, the IPASS study does not contribute any data in this patient population.

Missed Dose

If a dose of NAT-Gefitinib is missed, it should be taken as soon as the patient remembers, as long as it is at least 12 hours before the next dose is due. 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.

OVERDOSAGE

A limited number of patients were treated with daily doses of up to 1000 mg in phase I clinical trials. An increase in 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 (17 patients total / 3-4 patients per cohort) and twice weekly with doses from 1500 mg to 2000 mg (6 patients total / 3 patients per cohort). In this study, gefitinib exposure (mean Cmax) was approximately 3- to 4- fold that observed on multiple dosing of the therapeutic dose (i.e. 250 mg daily).

The mean QTcB appeared to increase approximately 10 msec at 3 hours postdose in 17 subjects receiving weekly doses of gefitinib. The study was not designed as a ‘thorough QTc’ study and

the QTc data should be approached with caution. No QTcB ≥ 500 msec was found during the study.

Adverse events were mostly mild to moderate in severity, and were consistent with the known safety profile of gefitinib. The frequency of some AEs, namely nausea, diarrhoea, vomiting, and fatigue appeared to have increased, however the patients enrolled in this study were end stage cancer patients with multiple confounding co-morbidities. Two out of the 6 patients in the twice weekly cohorts (one subject in Cohort 6 on 1500mg twice weekly; the other in Cohort 7 on 2000mg twice weekly) developed grade 3 total bilirubin increases however these were not reported as adverse events. Both of these patients had pre-existing liver metastases before start of treatment with gefitinib.

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

In non-clinical studies, the median lethal oral dose in rats was 2000 mg/kg (approximately 400 times the clinically recommended daily dose in humans on a mg/kg basis). The median lethal oral dose in mice was found to be in excess of 2000 mg/kg.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Gefitinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). EGFR is expressed on the cell surface of many normal cells as well as cancer cells. Increased EGFR signalling can drive tumour growth through the activation of pathways that are crucial to proliferation, invasion, angiogenesis, metastasis and inhibition of cell death.

Mutations in the tyrosine kinase domain of the EGFR gene are only found in tumour cells and increase the dependency of these tumour cells to the intercellular signalling cascades that result in the promotion of tumour cell growth, blocking of apoptosis, increasing the production of angiogenic factors and facilitating the processes of metastasis.

In patients whose tumour contains an activating mutation of the EGFR-tyrosine kinase (TK), gefitinib binds to the EGFR TK domain with high specificity and affinity, resulting in potent inhibition of the over-active signalling pathways which can lead to tumour shrinkage.

Resistance

Most NSCLC tumors 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 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.

Pharmacokinetics

The pharmacokinetics of gefitinib have been evaluated in healthy volunteers and in cancer patients following both single and multiple dosing.

Absorption: Following single oral administration to volunteers or to cancer patients, absorption was moderately slow and the mean terminal half-life was 30.5 and 41.0 hours, respectively. In volunteers, gefitinib AUC showed up to a 20-fold range at the same dose level and increased proportionally with dose over the dose range 50 to 250 mg. Between 250 and 500 mg, there was a slightly greater than dose proportional increase in exposure but the maximum degree of non-proportionality observed was only 2-fold. In cancer patients, gefitinib AUC increased with dose over the dose range 50 to 700 mg and showed up to an 8 fold range of values within a dose level.

Daily administration of gefitinib to patients resulted in a 2-to 8-fold accumulation with steady state plasma concentrations achieved within 7-10 days. At steady state, plasma concentrations were typically maintained within a 2-to 3-fold range across the 24-hour dosing interval. Population pharmacokinetic data from Trial 0016 showed a mean steady state trough concentration following a 250 mg oral dose of 264 ng/mL (95% CI: 92.2 to 755 ng/mL) with inter-and intra-patient variability of 54 and 21%, respectively.

Mean oral bioavailability of gefitinib was approximately 60% in both healthy volunteers and cancer patients, indicating that it was well absorbed. C_{max} was typically achieved within 3 to 7 hours after dosing in both groups. Relative bioavailability of gefitinib in volunteers was not altered by food to an extent likely to be of clinical significance. In a trial in healthy volunteers where gastric pH was maintained above pH 5 by co-administration of high doses of ranitidine with sodium bicarbonate, relative bioavailability was reduced by 47%.

Distribution: Mean volume of distribution at steady state of gefitinib is 1600 L in volunteers and 1400 L in cancer patients indicating extensive distribution into tissue. At clinically relevant concentrations of gefitinib, binding (in vitro) to human plasma proteins is approximately 90% with the binding proteins involved being 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. 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 Odesmethyl gefitinib, which was14-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 also 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 (devoid of CYP2D6) 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 and Conditions:

Paediatrics: There are no pharmacokinetic data in paediatric patients.

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

are related to dose and exposure to gefitinib (see WARNINGS AND PRECAUTIONS – Special Populations).

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 gefitinib 250 mg, time to steady state, total plasma clearance and steady state exposure (C_{maxss}, 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.

Renal Insufficiency: No clinical studies were conducted with gefitinib in patients with severely compromised renal function. Gefitinib and its metabolites are not significantly excreted via the kidney (<4%). A limited number of patients with moderate renal insufficiency (calculated creatinine clearance of 30-50 mL/min) participated in the clinical trials. Based on the data from these studies, no safety concerns were raised regarding the use of gefitinib in patients with mild or moderate renal impairment in comparison to patients with normal renal function at baseline. Due to the small number of patients, there is insufficient data to evaluate the safety profile of gefitinib in patients with severe renal impairment.

STORAGE AND STABILITY

NAT-GEFITINIB (gefitinib) should be stored at room temperature, 15°C to 30°C, keep in the original packaging, away from heat.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NAT-Gefitinib (gefitinib) are 250 mg brown coloured, round shaped, film coated tablets debossed with “N” on one side and “250” on other side. Available in blisters 30’s (3 x 10’s) tablets.

In addition to the active ingredient gefitinib 250 mg, each tablet contains the following nonmedicinal ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone K-30, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, yellow iron oxide and red iron oxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

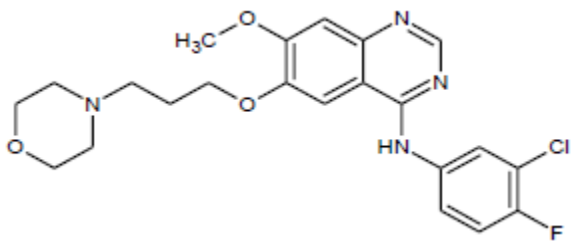
Proper Name: gefitinib

Chemical Name: N-(3-chloro-4-fluorophenyl-7-methoxy-6-[3(morpholin-4-yl) propoxy] quinazolin-4-amine)

Molecular Formula and Molecular Mass: $C_{22}H_{24}ClFN_4O_3$

446.9 g/mol

Structural Formula:



Physicochemical Properties:

Gefitinib is a white to off-white crystalline powder. Gefitinib is a free base. The molecule has pKa's of 6.5 and 6.9. Gefitinib can be defined as soluble at pH 1, but is practically insoluble above pH 3, with the solubility dropping after pH 3. In non-aqueous solvents, gefitinib is

freely soluble in dimethyl formamide, soluble in dimethyl sulphoxide, very slightly soluble in tetrahydrofuran, acetone, ethyl acetate and in ethanol, sparingly soluble in chloroform, slightly soluble in dichloromethane, insoluble in toluene and hexane.

CLINICAL TRIALS

A double blinded, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, oral comparative bioavailability study comparing NAT-Gefitinib (gefitinib) 250 mg tablet (Natco Pharma (Canada) Inc.) to PrIRESSA® (gefitinib) 250 mg tablet (AstraZeneca Canada Inc.) was conducted in 50 healthy male volunteers under fasting conditions. A summary of the bioavailability data from 45 volunteers who completed the study and whose data was included in the statistical analysis is presented in the following table.

Gefitinib (1 x 250 mg) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72} (hr*ng/mL)	4568.5 4968.4 (37.6)	4704.6 5061.1 (35.8)	96.0	87.2 - 105.7
AUC_T (hr*ng/mL)	5382.4 5927.9 (40.6)	5510.3 6002.0 (39.1)	96.5	87.6 - 106.4
AUC_I (hr*ng/mL)	5702.7 6318.4 (42.7)	5848.2 6436.1 (42.1)	96.4	87.6 - 106.0
C_{MAX} (ng/mL)	166.6 189.3 (48.9)	170.5 188.6 (40.5)	96.7	85.3 - 109.7
T_{MAX}§ (h)	5.8 (2.5 - 24.0)	6.0 (2.5 - 24.0)		
$T_{1/2}$@ (h)	32.0 (36.9%)	32.9 (44.4%)		

*NAT-Gefitinib (gefitinib) 250 mg tablets (Natco Pharma (Canada) Inc.)
†IRESSA® (gefitinib) 250 mg tablets (AstraZeneca Canada Inc.) were purchased in Canada.
§Expressed as the median (range) only.
@Expressed as the arithmetic mean (CV%) only.

First-line NSCLC Treatment

IPASS STUDY (D791AC00007)

Study demographics and trial design:

The efficacy and safety of gefitinib was demonstrated in a randomized, open-label, multicentre, Phase III trial versus carboplatin/paclitaxel doublet chemotherapy in the first line setting (IPASS). This study was conducted in Asia in patients with locally advanced or metastatic (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. A total of 1217 patients from 87 centres in China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan, and Thailand were studied. The primary efficacy endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), objective tumour response rate

(ORR), safety, quality of life (QoL) and symptom improvement. Statistical adjustment for multiplicity was not performed for secondary and exploratory endpoints.

Demographic and baseline characteristics were well balanced between the two treatment groups (see Table 5).

Table 5 Summary of demographic and disease characteristics/history: IPASS (ITT population)

Characteristic	Gefitinib 250 mg (N=609)	Carboplatin/Paclitaxel (N=608)
Age (years)		
Mean (SD)	56.5 (11.4)	56.8 (11.1)
Median	57.0	57.0
Range	24.0 to 84.0	25.0 to 84.0
Gender (n [%])		
Male	125 (20.5)	127 (20.9)
Female	484 (79.5)	481 (79.1)
Race origin (n [%])[a]		
Caucasian	3 (0.5)	1 (0.2)
Oriental	603 (99.0)	606 (99.7)
Other	3 (0.5)	1 (0.2)
Ethnic group (n[%])		
Asian[a]	179 (29.4)	184 (30.3)
Chinese	314 (51.6)	304 (50.0)
Japanese	114 (18.7)	119 (19.6)
Other[b]	2 (0.3)	1 (0.2)
Smoking history (n [%])		
Never smoked	571 (93.8)	569 (93.6)
Light ex-smoker	37 (6.1)	38 (6.3)
Ex-smoker (non-light)	1 (0.2)	1 (0.2)
WHO performance status		
0 (normal activity)	157 (25.8)	161 (26.5)
1 (restricted activity)	391 (64.2)	382 (62.8)
2 (in bed $\leq$50% of the time)	61 (10.0)	65 (10.7)
Tumour histology type		
Adenocarcinoma	581 (95.4)	591 (97.2)
Bronchoalveolar Carcinoma	27 (4.4)	15 (2.5)
Unknown[c]	1 (0.2)	2 (0.3)
Disease status (at entry)		
Locally advanced	150 (24.6)	144 (23.7)
Metastatic	459 (75.4)	463 (76.2)
Unknown	0 (0)	1 (0.2)
Time from diagnosis to randomization		
<6 months	582 (95.6)	573 (94.2)

Table 5 Summary of demographic and disease characteristics/history: IPASS (ITT population)

Characteristic	Gefitinib 250 mg (N=609)	Carboplatin/Paclitaxel (N=608)
≥ 6 months	27 (4.4)	34 (5.6)
Unknown	0 (0)	1 (0.2)
Stage classification (at diagnosis[d])		
IA	7 (1.1)	12 (2.0)
IB	2 (0.3)	9 (1.5)
IIA	2 (0.3)	1 (0.2)
IIB	1 (0.2)	6 (1.0)
IIIA	6 (1.0)	3 (0.5)
IIIB	166 (27.3)	163 (26.8)
IV	424 (69.6)	413 (67.9)
Unknown	1 (0.2)	1 (0.2)
Lesions present		
Target and non-target	570 (93.6)	557 (91.6)
Target only	39 (6.4)	50 (8.2)
Non-target only	0 (0)	1 (0.2)

[a] Patients belonging to Asian ethnic groups other than Chinese and Japanese.
[b] Indian (2 patients) and Punjabi (1 patient)
[c] One patient had small cell carcinoma, another had squamous cell carcinoma, and histology was not specified for another patient
[d] All patients had Stage IIIB or IV disease at entry.
ITT Intention-to-treat
N Number of patients
SD Standard deviation

Study results:

In the primary analysis of PFS in the intent-to-treat (ITT) population (see Table 6), the hazard ratio was not constant over time, with the probability of being progression-free in favour of carboplatin/paclitaxel doublet chemotherapy in the first 6 months, and in favour of gefitinib in the following 16 months. This was likely to be because of the different effect of gefitinib in subgroups defined by EGFR mutation status. EGFR activating mutation status was a strong predictive biomarker for the effect of gefitinib compared to carboplatin/paclitaxel. Patients with activating mutations of the EGFR-TK are referred to as patients with EGFR mutation positive tumours below.

Pre-planned exploratory biomarker analyses of 437 patients (36%) with evaluable data for EGFR mutation analysis were conducted.

PFS was significantly longer for gefitinib than carboplatin/paclitaxel in patients with EGFR mutation positive tumours (n=261, HR 0.48, 95% CI 0.36 to 0.64, p<0.0001), and significantly longer for carboplatin/paclitaxel than gefitinib in patients with EGFR mutation negative tumours (n=176, HR 2.85, 95% CI 2.05 to 3.98, p<0.0001).

ORR in patients with EGFR mutation positive tumours treated with gefitinib was 71.2% vs. 47.3% for patients with EGFR mutation positive tumours treated with carboplatin/paclitaxel (OR 2.75, 95% CI 1.654 to 4.60, p=0.0001). ORR in patients with EGFR mutation negative tumours treated with gefitinib was 1.1% vs. 23.5% in patients with EGFR mutation negative tumours treated with carboplatin/paclitaxel (OR 0.04, 95% CI 0.01 to 0.27, p=0.0013).

In patients with EGFR mutation positive tumours, significantly more gefitinib 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 patients with EGFR mutation negative tumours, significantly more carboplatin/paclitaxel treated patients experienced an improvement in QoL and lung cancer symptoms vs. gefitinib (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) in the overall study population, as well as in subgroups by EGFR mutation status (e.g. patients with EGFR mutation positive tumours and EGFR mutation negative tumours). Results of these analyses are shown in Table 6 as well as Figures 1 and 2.

Table 6 IPASS: Efficacy outcomes for Gefitinib versus carboplatin/paclitaxel

ITT Population	**N**	**Primary endpoint Progression Free Survival[a]**	**Objective Response Rate[a]**	**Overall Survival[a]**
Overall	1217	HR 0.74 [0.65, 0.85] 5.7m vs 5.8m P<0.0001	43.0% vs 32.2% OR 1.59 [1.25, 2.01] p=0.0001	HR 0.90 [0.79, 1.02] 18.8m vs 17.4m p=0.1087
EGFR Mutation positive	261	HR 0.48 [0.36, 0.64] 9.5m vs 6.3m P<0.0001	71.2% vs 47.3% OR 2.75 [1.65, 4.60] p=0.0001	HR 1.00 [0.76, 1.33] 21.6m vs 21.9m
EGFR Mutation negative	176	HR 2.85 [2.05, 3.98] 1.5m vs 5.5m p<0.0001	1.1% vs 23.5% OR 0.04 [0.01, 0.27] p=0.0013	HR 1.18 [0.86, 1.63] 11.2m vs 12.7m

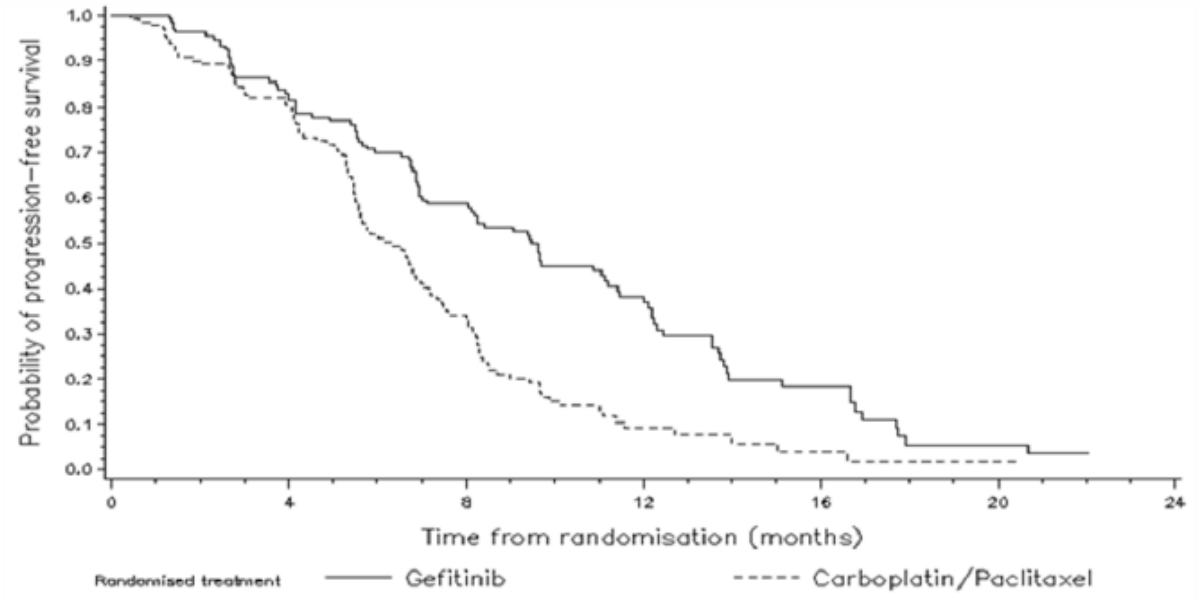
[a] Values presented are for gefitinib versus carboplatin/paclitaxel. 'm' is Medians in months. '%' is objective response rate (complete or partial response). Numbers in square brackets are 95% confidence intervals for HR or OR

N Number of patients randomised.

HR Hazard Ratio (hazard ratio <1 favours gefitinib)

OR Odds Ratio (odds ratio >1 favours gefitinib)

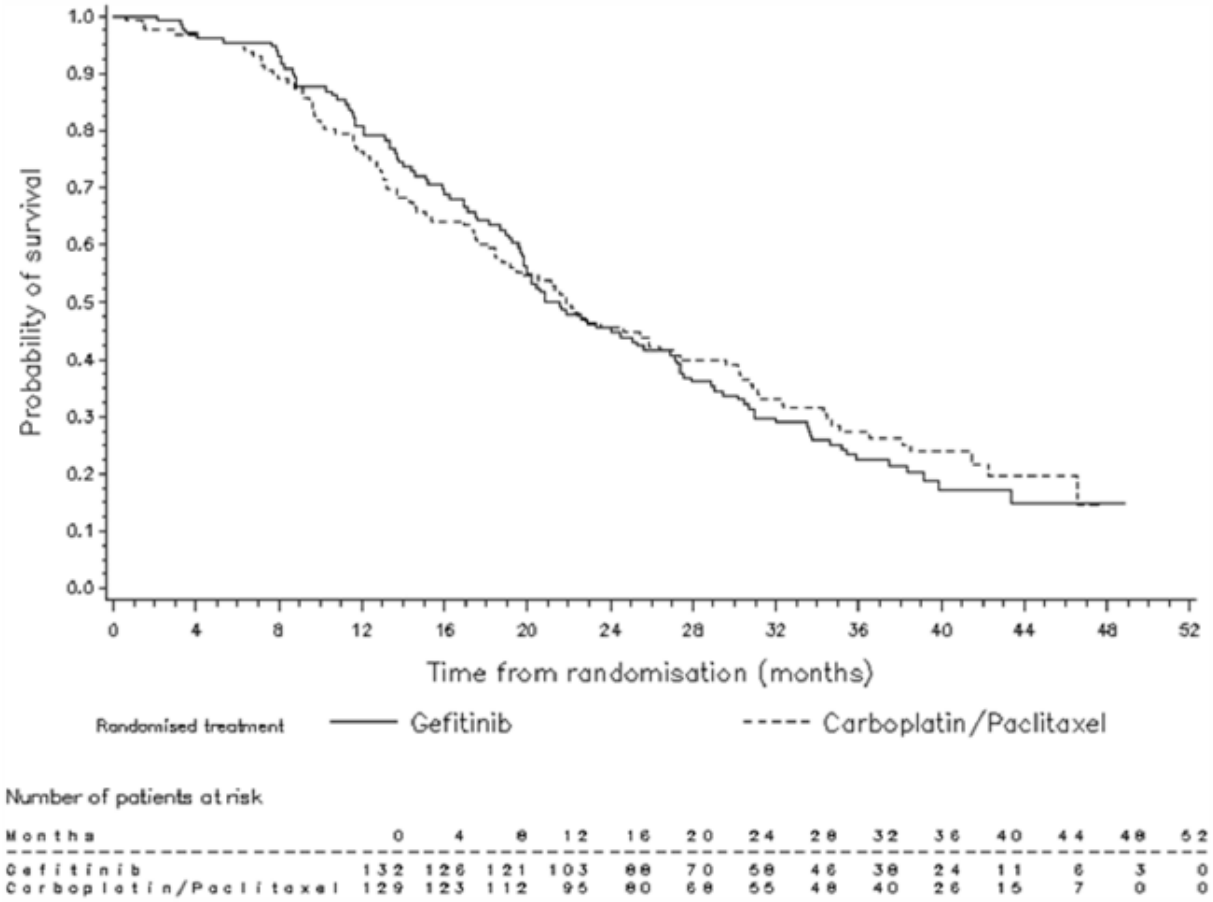
Figure 1 Kaplan-Meier curves for PFS: EGFR mutation positive subgroup



Number of patients at risk

Months	0	4	8	12	16	20	24
Gefitinib	132	108	71	31	11	3	0
Carboplatin/Paclitaxel	129	103	37	7	2	1	0

Figure 2 Kaplan-Meier curves for OS: EGFR mutation positive subgroup



When considering the OS data in the IPASS study, it is important to note that the majority of patients had received further systemic therapy following discontinuation of randomized first-line treatment, which is likely to confound assessment of the gefitinib treatment effect. Of the patients with EGFR mutation positive tumours randomized to gefitinib treatment, 68% received platinum based chemotherapy at some point post-discontinuation of randomized gefitinib, and 64% randomized to carboplatin/paclitaxel received EGFR TKI at some point post discontinuation of carboplatin/paclitaxel.

In the IPASS study, a number of exploratory analyses of PFS, ORR and OS for subgroups were performed, including post-hoc analyses by EGFR mutation subtypes (exon 19 deletions and exon 21 L858R mutations) within the subgroup of patients with EGFR mutation positive tumours. The PFS, ORR and OS data for the comparison of gefitinib vs. carboplatin/paclitaxel were; in patients with exon 19 deletions (N=140 patients), PFS HR=0.38 (95% CI 0.26 to 0.56), ORR=84.8% vs. 43.2% [OR 7.23 (95% CI, 3.19 to 16.37)] and OS HR 0.79 (95% CI 0.54 to 1.15) (median OS 27.2 months vs. 20.6 months); and in patients with exon 21 L858R mutations (N=111 patients), PFS HR=0.55 (95% CI 0.35 to 0.87), ORR=60.9% vs. 53.2% [OR 1.41 (95% CI, 0.65 to 3.05)] and OS HR=1.44 (95% CI 0.90 to 2.30) (median OS 18.7 months vs. 24.6

months). The study was not designed and powered to evaluate the differential PFS, ORR and OS by mutation subtypes, therefore the data should be interpreted in such context with caution.

Pre-treated NSCLC

INTEREST STUDY (D791GC00001)

INTEREST was a Phase III, randomized, open-label, parallel-group, international, multicentre trial comparing gefitinib to docetaxel in 1466 patients with locally advanced or metastatic NSCLC who had previously received platinum-based chemotherapy and were eligible for further chemotherapy. Pre-planned exploratory subgroup analysis of 44 EGFR mutation positive patients provides supportive evidence for the approved indication. For patients with EGFR mutations, gefitinib was superior to docetaxel in terms of PFS (HR 0.16, 95% CI 0.05 to 0.49, p=0.0012) and ORR (42.1% vs 21.1%, p=0.00361).

NSCLC - Studies of Gefitinib in Combination with Chemotherapy

Controlled trials (INTACT I and II) with first-line treatment of NSCLC indicated no benefit from the addition of gefitinib to platinum based combined chemotherapies.

DETAILED PHARMACOLOGY

Pharmacodynamics

In vitro

ZD1839 was tested using a cloned potassium channel assay (hERG assay) to evaluate its effect upon the Ikr potassium current and was shown to be active in this hERG assay, with an IC50 of 1 mM. Dog Purkinje fibre studies were undertaken to investigate the potential for ZD1839 to affect the cardiac action potential. The results indicate a modest potential to affect re-polarisation at high plasma concentrations. There is some evidence for in vivo effects, in the conscious telemetered dog, however these were not clear even at the highest dose tested.

In vivo

ZD1839 has been administered orally at 5, 50 and 500 mg/kg to rats in studies designed to evaluate its effect on the major functional systems. These included the gastrointestinal (rat, GI transit), respiratory (rat, plethysmography), central nervous (rat, Functional Observation Battery and locomotor activity) and cardiovascular (dog, telemetry, only at 5 and 50 mg/kg) systems.

No effects were seen on intestinal transit. Minimal effects were noted at 50 and 500 mg/kg on the respiratory system (decreases in peak inspiratory and expiratory flows, tidal volume and minute volume); on the central nervous system (slight reduction in motor activity); and on the cardiovascular system (dog telemetry at doses of 50 mg/kg showed slight hypotension).

Because the doses studied are higher than the clinically recommended dose, the effects seen in these studies are not likely to be clinically relevant, but caution is advised.

Pharmacokinetics

In vivo

ZD1839 is well absorbed in rat, dog and man based on measured bioavailabilities of >40% in all species. There is evidence of first pass metabolism and prolonged absorption at high doses in animals.

ZD1839 related radioactivity was well distributed into rat tissues and showed an association with melanin containing tissues; however, levels in the CNS were low. Plasma protein binding ranged from 86 to 94% across the species and is not concentration dependent. ZD1839 binds to both human serum albumin and α-1 acid glycoprotein.

ZD1839 was extensively metabolized with three sites of biotransformation. Circulating metabolite patterns in dog and man were similar and all metabolites measured in human plasma were present in the rat. ZD1839 showed no enzyme induction potential in animals and no appreciable inhibition of human P450 isozymes. *In vitro*, ZD1839 was predominantly metabolized by CYP3A4.

In all species, ZD1839 related material was primarily excreted in the faeces with <6.5% recovered in urine. Biliary elimination was demonstrated in the rat and enterohepatic recirculation of ZD1839 may occur.

In rat and dog, ZD1839 showed rapid clearance and a high volume of distribution. In man, the volume of distribution was greater than in animals and the half-life consequently longer leading to accumulation. When dose normalized, exposure in humans was greater than in rat and dog, but at chronically tolerated doses the exposures were comparable.

The pharmacokinetic parameters for ZD1839 in animals and man are summarized below:

Table 7 Comparison of Pharmacokinetic Parameters in Rat, Dog and Man

Parameter	Male rat[a]	Female rat[a]	Dog[b]	Human[c]
CL (ml/min/kg)	42.0 - 25.2	23.6 - 16.1	10.6 -16.1	11.9
Vss (l/kg)	9.2 - 10.4	9.8 - 8.0	2.1 - 6.3	28.0
T ½ (h)	3 - 13.8	5 - 8.2	3.4 - 7.8	48

[a]Values for study KKR008 and KPR055 respectively.

[b]Values from study KKD009 and KPD050 respectively.

[c]Mean data from IL/0035 normalized using a 50 kg body weight.

TOXICOLOGY

A standard programme of non-clinical safety evaluation studies of up to 6 months in duration has formed the basis of the support for the clinical development of once daily oral therapy to patients.

The no-effect dose level, after administration of ZD1839 for up to 1 month, is 2 mg/kg/day and over a 6 month period is 1 mg/kg/day. In the 1-month studies, a dose of 40 mg/kg/day produced pathological changes in the ovaries of rats and in the eyes, kidneys and skin of both rats and dogs. Loose faeces were recorded in dogs, with no associated histopathological correlate. Similar

changes were detected in the 6-month studies and, in addition in rats, minimal/mild hepatocellular necrosis was also detected, together with increased levels of circulating plasma liver enzymes. These effects showed signs of partial or full reversibility after drug withdrawal. There was evidence of reduced fertility in the female rat at 20 mg/kg/day, as well as slight maternal and fetotoxicity in the rabbit. These changes were all attributed to the pharmacological effects of ZD1839 on EGF-dependent tissues. Reversible abnormalities of atrio-ventricular conduction were also seen in the dog, at 40 mg/kg/day in the 1-month study and at 15 mg/kg/day in the 6-month study.

Preclinical work in guinea pigs indicates that gefitinib may be a potential skin (contact) sensitizer. Results of an in vitro phototoxicity study demonstrated that gefitinib may have phototoxicity potential.

Acute Toxicity

Following a single oral dose of ZD1839 at 2000 mg/kg to rats, there was a 5-day interval prior to the onset of abnormal signs. All animals showed adverse signs, leading to 4 premature deaths in females. The cause of death of 1 of these 4 decedents was a perforated duodenal ulcer. Other compound-related findings were present in tissues of these animals, including the kidneys, liver, skin and upper gastro-intestinal tract. No abnormalities were seen in mice given the same oral dose nor in rats and mice at the maximum achievable dose of 20 mg/kg by the intravenous route. Single oral doses of up to 1000 mg/kg to dogs produced no deaths, but caused adverse effects that had a rapid onset, but were reversible. These effects comprised emesis, diarrhoea, loss of skin tone, reduced blood pressure, reduced appetite, loss of body weight and increased plasma ALT, AST and ALP activities.

Multiple Dose Toxicity Studies

The no effect dose level after administration of ZD1839 to rats and dogs for up to 1 month was 2 mg/kg/day. A dose of 10 mg/kg/day showed only minor changes in red blood cell parameters, plasma protein, and albumin in the 1-month dog study and no adverse effects in the 1-month rat study. A dose of 40 mg/kg/day in the rat for a month produced reversible increases in plasma ALT and AST levels, but with no pathological correlate. There were histopathological changes in the ovaries of rats (reduced corpora lutea) and in the eyes (corneal epithelial atrophy), kidneys (papillary necrosis), and skin of both rats and dogs, all of which showed signs of partial or full reversibility, 4 weeks after drug withdrawal. Loose faeces were recorded in dogs, with no associated histopathological correlate. These changes were attributed to the pharmacological effects of ZD1839. Reversible prolonged PR intervals, with large variations between individual measurements were recorded for 2 out of 12 dogs at 40 mg/kg/day. In addition, one of these two dogs also showed second-degree heart block.

The findings in the 6-month studies were consistent with those detected in the 1-month studies and were similarly attributed to the pharmacological effects of ZD1839. These studies commenced with a high dose of 25 mg/kg/day, however this was not tolerated and the dose level was reduced to 15 mg/kg/day from day 11 in dogs and from week 9 in rats. The no adverse effect dose level, after administration of ZD1839 to rats and dogs for up to 6 months was 1 mg/kg/day. At 5 mg/kg/day, rats and dogs showed skin lesions and the rats had reversible corneal atrophy of the eyes. These eye effects were more evident in both species at 15 mg/kg/day, but still showed signs of recovery. However, at this dose level in dogs, some areas of opacity developed that did

not fully recover during the 12 week withdrawal period. Evidence of an effect on liver function was detected in the rat at 5 mg/kg/day; this was more pronounced in both species at 15 mg/kg/day. In addition, in the rat at this dose, there was hepatocellular necrosis, associated with the increases in plasma liver enzyme levels. A single female dog showed evidence of a reversible effect on P-R interval, similar to that seen in the 1 month study, at the 15 mg/kg/day dose level.

Carcinogenicity & Mutagenicity

ZD1839 has been tested for genotoxic activity (mutagenicity) in a series of *in vitro* (bacterial mutation, mouse lymphoma, and human lymphocyte) assays and an *in vivo* rat micronucleus test. Under the experimental conditions adopted, there was no evidence demonstrated of genotoxic activity for ZD1839.

A 2 year oral (gavage) 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 high dose (10 mg/kg/day) only. The clinical relevance of these findings is unknown. The hepatocellular adenomas were also seen in a 2 year oral (gavage) 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.

Reproduction & Teratology

There was, as expected from the pharmacological activity of ZD1839, a reduction in female fertility in the rat at a dose of 20 mg/kg/day. Gefitinib has been found to cross the placenta following oral administration at 5 mg/kg in rats. 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 fetal weights at 20 mg/kg/day and above. There were no compound induced malformations in either species. When pregnant rats that were treated with 5 mg/kg/day from the beginning of organogenesis to the end of weaning gave birth, there was a reduction in the number of offspring born alive. In pregnant rats treated with 20 mg/kg/day, the effects were more severe and included high neonatal mortality. The no observed adverse effect dose level in this study was 1 mg/kg/day. There was evidence that ZD1839 was present in the milk of lactating rats. Following oral administration of carbon-14 labelled gefitinib to rats 14 days postpartum, concentrations of radioactivity in milk were higher than in blood. Levels of gefitinib and its metabolites were 11- to 19-fold higher in milk than in blood, after oral exposure of lactating rats to a dose of 5 mg/kg. These data suggest that there is the potential for adverse effects if ZD1839 was administered to patients who are pregnant or are breast-feeding.

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22. Product Monograph PrIRESSA® - Gefitinib Tablets 250 mg (Epidermal Growth Factor Receptor [EGFR] Tyrosine Kinase Inhibitor) - AstraZeneca Canada Inc. Control No:205832, Date of Revision: September 25, 2017.

PART III: CONSUMER INFORMATION

[Pr]NAT-Gefitinib

Gefitinib Tablets

This leaflet is part III of a three-part "Product Monograph" published when NAT-Gefitinib was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NAT-Gefitinib.

Contact your doctor or pharmacist if you have any questions about the drug.

Read all of this leaflet carefully before you start taking NAT-Gefitinib. Keep this leaflet. You may need to read it again.

ABOUT THIS MEDICATION

What NAT-Gefitinib is used for:
NAT-Gefitinib is used for the initial treatment of adult patients with non-small cell lung cancer (NSCLC) that is locally advanced (not suitable for a curative therapy) or metastatic (when cancer cells have spread from the lung to the other part of the body) who have activating mutations of the Epidermal Growth Factor Receptor tyrosine kinase (EGFR-TK).

What NAT-Gefitinib does:
NAT-Gefitinib works by attaching to Epidermal Growth Factor Receptors (EGFRs) on the surface of cancer cells and blocking the signalling from EGFRs that are involved in the growth and spread of cancer cells. NAT-Gefitinib works only in non-small cell lung cancer cells that have a mutation in their EGFRs.

Do not use NAT-Gefitinib if:
- You are allergic to gefitinib or any of the other ingredients of NAT-Gefitinib.

What the medicinal ingredient is:
Gefitinib

What the nonmedicinal ingredients are:
Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone K-30, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, yellow iron oxide and red iron oxide.

What dosage forms NAT-Gefitinib comes in:
NAT-Gefitinib is an oral tablet and each tablet contains 250 mg gefitinib. NAT-Gefitinib comes in blisters 30's (3 x 10's) tablets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

NAT-Gefitinib should be prescribed by a health care professional experienced in the treatment and management of patients with cancer.

NAT-Gefitinib should not be used in patients with EGFR mutation negative tumours.

NAT-Gefitinib has not been studied in patients with severely reduced kidney function.

Isolated cases of liver failure have been reported in patients taking gefitinib, and some patients have died from this.

Gastrointestinal perforation (a hole through the wall of the stomach or intestine), including fatal cases, was reported in patients taking gefitinib.

Before you use NAT-Gefitinib, talk to your doctor or pharmacist if:

- You have, or have had, lung diseases other than lung cancer. Some of them may worsen during treatment with NAT-Gefitinib.
- You are pregnant, or plan to become pregnant.
- You are breastfeeding.
- You have a disorder affecting the liver.
- You have eye problems or wear contact lenses.
- You have kidney problems.
- You smoke, are at an advanced age, have a history of gastrointestinal ulceration, have cancer that has spread to the bowel, or are

taking steroids or non-steroidal anti-inflammatory drugs.

Bleeding has been reported with the use of gefitinib such as nosebleed, blood in the urine, coughing up of blood and bleeding from the lungs.

NAT-Gefitinib is not expected to impair your ability to drive or use machines. However, some patients may occasionally feel weak. If this happens, you should not drive or operate machinery.

NAT-Gefitinib is not recommended for use in patients under 16 years of age.

INTERACTIONS WITH THIS MEDICATION

Please inform your doctor if you are taking or have taken any medicines (including medicines taken some time ago), even those available over the counter.

Your doctor especially needs to know if:

- You take any of the following medicines: phenytoin, carbamazepine, rifampicin, barbiturates, St John's Wort, itraconazole, ketoconazole, protease inhibitors (drugs to treat HIV/AIDS) or macrolide antibiotics such as erythromycin or clarithromycin. These medicines may affect the way NAT-Gefitinib works. Your doctor should also know if you drink grapefruit juice.
- You take warfarin (to prevent blood-clots), as NAT-Gefitinib may affect it. Your doctor may need to check your blood more often.
- You take any medicines which are used to help reduce stomach acid (e.g., ranitidine, sodium bicarbonate, proton-pump inhibitors).

PROPER USE OF THIS MEDICATION

Usual dose:

Take one 250 mg tablet, once a day, every day, at about the same time. You can take NAT-Gefitinib with or without food.

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Overdose:

If you think you have taken too much NAT-Gefitinib, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, take the last missed dose as soon as you remember, as long as it is at least 12 hours before the next dose is due.

If it is less than 12 hours until the next dose, do not take the dose you have missed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, NAT-Gefitinib can have side effects. These are usually mild to moderate in intensity, and reversible. Side effects often start during the first month of taking NAT-Gefitinib.

Talk to your doctor if any of the following happens to you. You may need further examinations or treatment:

Very common side effects (Greater than or equal to 10 of every 100 patients):

- Diarrhea, nausea, vomiting, stomatitis (red and sore mouth)
- Loss of appetite
- Skin reactions such as rash, itching dry and/or cracked skin
- Weakness (asthenia)

Common side effects (Greater than or equal to 1 every 100 patients, but less than 10 of every 100 patients):

- Dry mouth
- Nosebleed or blood in the urine
- Protein in your urine (shown in a urine test)

- Burning sensations during urination and frequent, urgent need to urinate (cystitis)
- Nail problems
- Loss of hair
- Eye problems (dry, red, itchy eye or red and sore eyelid)
- Fever

Uncommon side effects (Greater than or equal to 1 of every 1000 patients, but less than 1 of every 100 patients):

- Unexpected bleeding if you are taking warfarin.

The following side effects can also occur with NAT-Gefitinib, and they are seen when a blood test is taken:

Very common (Greater than or equal to 10 of every 100 patients):

- Changes to the level of one liver enzyme known as alanine aminotransferase (ALT).

Common (Greater than or equal to 1 every 100 patients, but less than 10 of every 100 patients):

- Changes to the level of bilirubin and the other liver enzyme known as aspartate aminotransferase (AST).
- Changes to the level of creatinine in your blood, which shows how well your kidneys are working. This is often a consequence of diarrhea or vomiting, which may lead to severe dehydration.

Uncommon (Greater than or equal to 1 of every 1000 patients, but less than 1 of every 100 patients):

- Changes to the way your blood clots, if you are taking warfarin (medicine to prevent blood-clotting).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM	
Symptom / effect	Talk with your doctor or pharmacist in all cases
Common (Greater than or equal to 1 every 100 patients, but less than 10 of every 100 patients)	
Dehydration following persistent or severe diarrhoea, vomiting, nausea (feeling sick), or loss of appetite. Dehydration may lead to renal dysfunction if left untreated.	√
Serious breathlessness, or sudden worsening breathlessness, possibly with a cough or fever. Some patients taking NAT-Gefitinib get an inflammation of the lungs called interstitial lung disease and some patients have died from this.	√
Uncommon (Greater than or equal to 1 of every 1000 patients, but less than 1 of every 100 patients)	
New eye problems, such as pain, redness, watery eyes, light sensitivity, or changes in vision. Ulcers on the surface of the eye (cornea), sometimes with in-growing eyelashes have been observed.	√
Inflammation of the pancreas with symptoms such as very severe pain in the upper part of the stomach area and severe nausea (feeling sick) and vomiting.	√
Allergic reactions, including swelling of the lips and hives or nettle-rash.	√
Inflammation of the liver or liver failure. Symptoms may include a general feeling of being unwell, nausea, vomiting, with or without possible jaundice (yellowing of the skin and eyes).	√
Gastrointestinal perforation (a hole through the wall of the stomach or intestine, which may be detected by X-Ray or scan); some patients have died from this.	√
Rare (greater than or equal to 1 in every 10000, but less than 1 in every 1000 patients)	
Inflammation of the blood vessels in the skin. This may give the appearance of bruising or patches of non-blanching rash on the skin.	√
Severe skin reactions affecting large portions of the body including redness, pain, ulcers, blisters, skin sloughing or involvement of lips and mucous membranes (toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme).	√
Burning sensations during urination and frequent, urgent need to urinate with blood in the urine (hemorrhagic cystitis)	√

This is not a complete list of side effects. For any unexpected effects while taking NAT-Gefitinib, contact your doctor or pharmacist.

Date prepared: August 22, 2019

HOW TO STORE IT

Keep out of the reach and sight of children.

Store at room temperature, 15°C to 30°C, keep in the original packaging, away from heat.

Do not use NAT-Gefitinib after the expiry date on the blister pack.

Remember to return any unused NAT-Gefitinib to your pharmacist.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

-Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html for information on how to report online, by mail or by fax; or
-Calling toll-free 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about NAT-Gefitinib:
-Talk to your healthcare professional
-Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html) ; the manufacturer's website www.natcopharma.ca, or by calling 1-800-296-9329.

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