PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]NAT-GEFITINIB

Gefitinib Tablets

Tablets, 250 mg

Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor

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RECENT MAJOR LABEL CHANGES

Not Applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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 7 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 14 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (≤ 16 years of age): Gefitinib is not indicated for use in pediatric patients, as safety and effectiveness have not been established (see 7 WARNINGS AND PRECAUTIONS – 7.1 Special Populations).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No differences in safety or efficacy were observed between younger and older patients (see 7 WARNINGS AND PRECAUTIONS – 7.1 Special Populations).

2 CONTRAINDICATIONS

Gefitinib is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 7 WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests and 14 CLINICAL TRIALS sections).
- NAT-GEFITINIB has not been studied in patients with severe renal impairment (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics – Special Populations and Conditions).
- Isolated cases of hepatic failure and fulminant hepatitis, including fatalities, have been reported with gefitinib use (see 7 WARNINGS AND PRECAUTIONS – Hepatotoxicity).
- Gastrointestinal perforation (including cases with a fatal outcome) was observed in patients treated with gefitinib (see 7 WARNINGS AND PRECAUTIONS – Gastrointestinal)

4 DOSAGE AND ADMINISTRATION

4.2 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.

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 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics – 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 diarrhea: Patients with poorly tolerated diarrhea (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 dyspnea, 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 7 WARNINGS AND PRECAUTIONS - Respiratory and 8 ADVERSE REACTIONS sections).

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 7 WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic and 10 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.

Pediatric Use: Health Canada has not authorized an indication for pediatric use, as safety and effectiveness have not been established (see 1 INDICATIONS – 1.1 Pediatrics and 7 WARNINGS AND PRECAUTIONS – 7.1 Special Populations).

4.4 Administration

NAT-GEFITINIB is for oral use only.

4.5 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.

5 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 diarrhea 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, diarrhea, 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 1500 mg twice weekly; the other in Cohort 7 on 2000 mg 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 diarrhea

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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet / 250 mg	croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone K-30, red iron oxide, sodium lauryl sulphate, talc, titanium dioxide, and yellow iron oxide.

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.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis

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 16 NON-CLINICAL TOXICOLOGY – Carcinogenicity).

Cardiovascular

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 10 CLINICAL PHARMACOLOGY – 10.2 Pharmacodynamics).

Driving and Operating 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.

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 4 DOSAGE AND ADMINISTRATION – 4.2 Recommended Dose and Dosage 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.

Hematologic

International Normalized 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 9 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.

Hemorrhage

Throughout the gefitinib lung cancer clinical trials, the incidence of hemoptysis/pulmonary hemorrhage 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 hematuria 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.

Hepatic Impairment

Patients with moderate to severe hepatic impairment (Child Pugh B or C) due to cirrhosis have increased plasma concentrations of gefitinib (see 10 CLINICAL PHARMACOLOGY and 4 DOSAGE AND ADMINISTRATION sections). 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.

Monitoring and Laboratory Tests

Assessment of EGFR Mutation Status: EGFR mutation status must be known prior to starting gefitinib therapy because only patients with an activating mutation of EGFR TK should be treated with gefitinib (see 1 INDICATIONS and 14 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 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 9 DRUG INTERACTIONS).

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 8 ADVERSE REACTION). If a diagnosis of ulcerative keratitis is confirmed, treatment with gefitinib should be interrupted, and if symptoms do not resolve, or recur on reintroduction of gefitinib, permanent discontinuation should be considered.

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 4 DOSAGE AND ADMINISTRATION – 4.2 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), 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 8 ADVERSE REACTIONS – Interstitial Lung Disease).

If patients present with worsening of respiratory symptoms such as dyspnea, 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 8 ADVERSE REACTIONS – Interstitial Lung Disease). In a Japanese Pharmacoepidemiological case-control study (see 8 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%).

Sensitivity/Resistance

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.

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 4 DOSAGE AND ADMINISTRATION – 4.2 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.

7.1 Special Populations

7.1.1 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 may cause fetal harm when administered to a pregnant woman (See 16 NON-CLINICAL TOXICOLOGY - Reproductive and Developmental Toxicology).

7.1.2 Breast-feeding

It is not known whether gefitinib is excreted in human milk, however this is documented to occur in pre-clinical testing (See 16 NON-CLINICAL TOXICOLOGY - Reproductive and Developmental Toxicology). 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.

7.1.3 Pediatrics

Pediatrics (≤ 16 years of age): In a Phase I/II trial of gefitinib and radiation in pediatric patients, newly diagnosed with brain stem glioma or incompletely resected supratentorial malignant glioma, 4 cases (1 fatal) of CNS hemorrhages have been reported in 45 patients enrolled. A further case of CNS hemorrhage has been reported in a child with an ependymoma from a trial with gefitinib alone. An increased risk of cerebral hemorrhage in adult patients with NSCLC receiving gefitinib has not been established. NAT-GEFITINIB is not indicated for use in pediatric patients, as safety and effectiveness have not been established.

7.1.4 Geriatrics

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.

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 (see 9 DRUG INTERACTIONS).

8 ADVERSE REACTIONS

8.1 Adverse 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 diarrhea, 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 and Table 4 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 14 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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

System Organ Class Preferred term	Percentage (%) of Patients with Adverse Reactions
Eye disorders	
Conjunctivitis, blepharitis, and dry eye*, mainly mild in nature (CTC grade 1).	6.7
Gastrointestinal disorders	
Diarrhea, mainly mild or moderate in nature (CTC grade 1 or 2) and, less commonly, severe (CTC grade 3 or 4).	34.9
Nausea, mainly mild in nature (CTC grade 1).	17.8
Vomiting, mainly mild or moderate in nature (CTC grade 1 or 2).	13.8
Stomatitis, predominantly mild in nature (CTC grade 1)	11.0
Dry mouth*, predominantly mild in nature (CTC grade 1)	2.0
Dehydration, secondary to diarrhea, nausea, vomiting or anorexia	1.8
General Disorders and administration site conditions	
Asthenia, predominantly mild in nature (CTC grade 1)	17.7
Pyrexia	8.7
Hepatobiliary disorders	
Elevations in alanine aminotransferase, mainly mild to moderate	11.4
Elevations in aspartate aminotransferase, mainly mild to moderate	7.9
Elevations in total bilirubin, mainly mild to moderate	2.7
Metabolism and nutrition disorders	
Anorexia, mild or moderate in nature (CTC grade 1 or 2)	19.7

System Organ Class Preferred term	Percentage (%) of Patients with Adverse Reactions
Renal and urinary disorders	
Proteinuria	7.7
Asymptomatic laboratory elevations in blood creatinine	1.5
Cystitis	1.1
Respiratory, thoracic and mediastinal disorders	
Interstitial lung disease, often severe (CTC grade 3-4). Fatal outcomes have been reported.	1.3
Skin and subcutaneous tissue disorders	
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	57.9
Nail disorder	7.9
Alopecia	4.7
Allergic reactions**, including angioedema and urticaria	1.1
Vascular disorders	
Haemorrhage, such as epistaxis and haematuria	4.3

* 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.

IPASS STUDY (D791A00007)

In IPASS, the most commonly reported adverse events for patients treated with gefitinib were diarrhea 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]		
Anemia	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		
Diarrhea	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	47 (7.7)	186 (31.6)
Myalgia	39 (6.4)	113 (19.2)
Arthralgia		

System organ class and preferred term	Number (%) of patients[a]	
	Gefitinib 250 mg (N=607) Overall[b]	Carboplatin/ Paclitaxel (N=589) Overall[b]
Nervous system disorders		
Peripheral sensory neuropathy	23 (3.8)	141 (23.9)
Hypoesthesia	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)
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 > 3 (worsenings from baseline only) occurring during the period on randomized treatment (Table 3). Events of rashes/acnes, diarrhea and CTC Grade > 3 liver transaminases were reported at a statistically significantly

higher incidence in the gefitinib arm. Events of neurotoxicity, and CTC Grade ≥ 3 hematological toxicity (CTC Grade ≥ 3 neutropenia, leukopenia, thrombocytopenia, and anemia) 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)

	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
Diarrhea	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 ≥ 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 ≥ 3)[c]	4	(0.7)	385	(65.4)	<0.0001
Leukopenia (CTC ≥ 3)[c]	1	(0.2)	202	(34.3)	<0.0001
Anemia (CTC ≥ 3)[c]	11	(1.8)	56	(9.5)	<0.0001
Thrombocytopenia (CTC ≥ 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 14 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 7 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).

8.3 Less Common Clinical Trial Adverse Reactions

Table 4 Adverse Drug Reactions by frequency and system/organ (pooled safety data from ISEL, INTEREST and IPASS phase III clinical trials)

System Organ Class Preferred term	Percentage (%) of Patients with Adverse Reactions
Eye disorders	
Corneal erosion [reversible and sometimes in association with aberrant eyelash growth]	0.3
Keratitis	0.1
Gastrointestinal disorders	
Gastrointestinal perforation	0.2
Pancreatitis	0.1
Hepatobiliary disorders	
Hepatitis*	0.2
Renal and urinary disorders	
Hemorrhagic cystitis	**
Skin and subcutaneous tissue disorders	
Bullous conditions including, toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme	0.04
Cutaneous vasculitis	**

* 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.

8.5 Post-Market Adverse 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 and palmar-plantar erythrodysesthesia syndrome.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Table 5 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.

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, but has potential to inhibit CYP2D6. 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; dose modification of the CYP2D6 substrate should be considered and caution is advised when co-administered with 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.

Drugs that cause significant sustained elevation in gastric pH may reduce plasma concentrations of NAT-GEFITINIB and therefore may reduce efficacy.

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 10 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.

9.5 Drug-Food Interactions

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

9.6 Drug-Herb Interactions

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

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

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.

Animal Studies – *In vitro*

Gefitinib 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 gefitinib 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.

Animal Studies - *In vivo*

Gefitinib 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.

10.3 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. Cmax 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 fecal extracts and the major component was O-desmethyl gefitinib, although this only accounted for 14% of the dose.

In human plasma, 8 metabolites were fully identified. The major metabolite identified was O-desmethyl gefitinib, which 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.

Elimination

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

Special Populations and Conditions

- **Pediatrics:** There are no pharmacokinetic data in pediatric 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 7 WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic).

  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.

11 STORAGE, STABILITY AND DISPOSAL

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

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

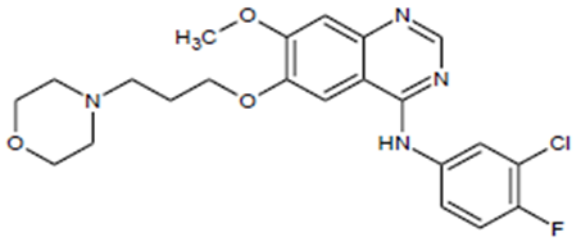
Drug Substance

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: $C_{22}H_{24}ClFN_4O_3$ and 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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

First-line NSCLC Treatment: IPASS STUDY (D791AC00007)

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 6):

Table 6 - 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)
≥ 6 months	27	(4.4)	34	(5.6)
Unknown	0	(0)	1	(0.2)
Stage classification (at diagnosis[d])				

Characteristic	Gefitinib 250 mg (N=609)		Carboplatin/Paclitaxel (N=608)	
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

14.2 Study Results

First-line NSCLC Treatment: IPASS STUDY (D791AC00007)

In the primary analysis of PFS in the intent-to-treat (ITT) population (see Table 7), 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 7 as well as Figures 1 and 2.

Table 7 - 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

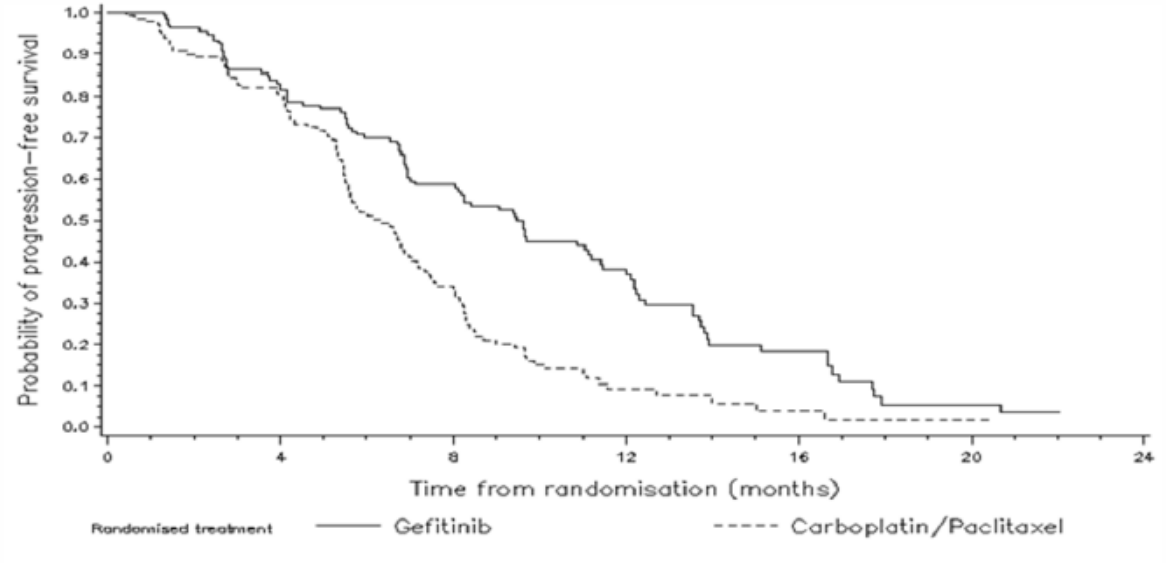
[a] Values presented are for gefitinib versus carboplatin/paclitaxel. 'm' is Medians in months. '%' is objective response rate (complete or partial response). Numbers in square brackets are 95% confidence intervals for HR or OR

N Number of patients randomized.

HR Hazard Ratio (hazard ratio <1 favours gefitinib)

OR Odds Ratio (odds ratio >1 favours gefitinib)

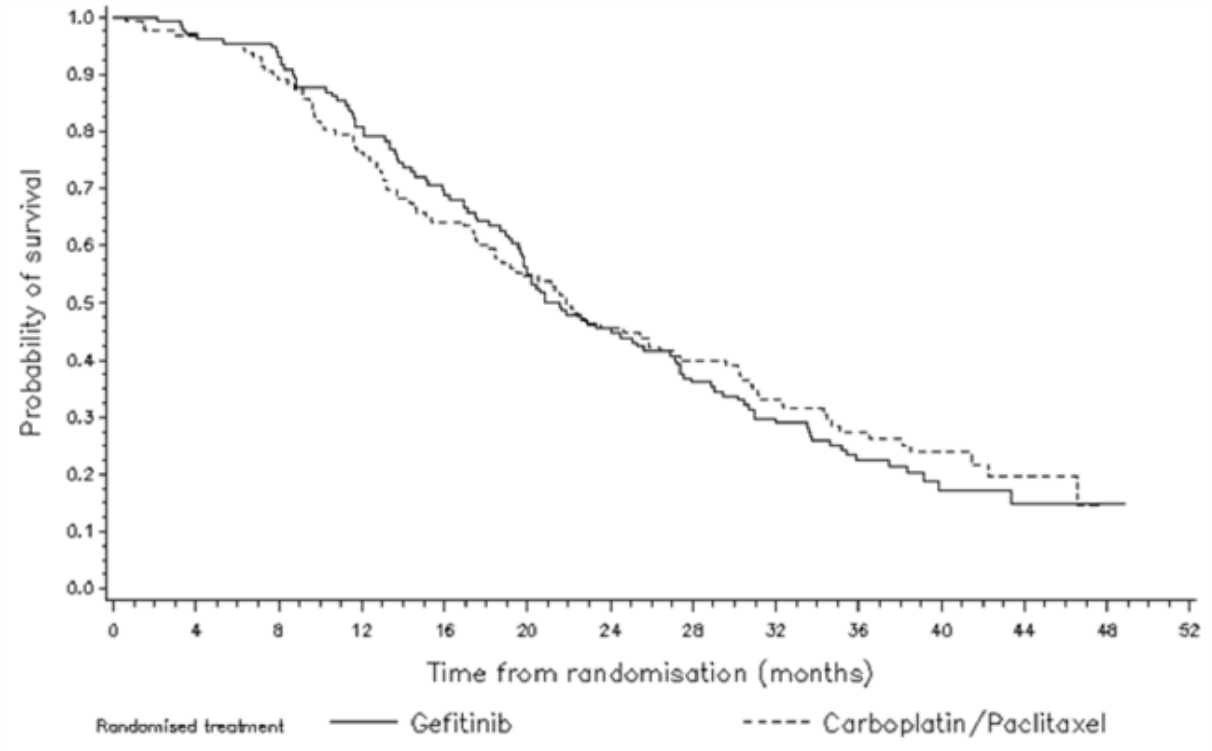
Figure 1 Kaplan-Meier curves for PFS: EGFR mutation positive subgroup



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



Number of patients at risk

Months	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Gefitinib	132	126	121	103	88	70	58	46	38	24	11	6	3	0
Carboplatin/Paclitaxel	129	123	112	95	80	68	55	48	40	26	15	7	0	0

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.

14.3 Comparative Bioavailability Studies

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[1]**	**Reference[2]**	**% 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}[3] (h)	5.8 (2.5 - 24.0)	6.0 (2.5 - 24.0)	Not applicable	Not applicable
$T_{½}$[4] (h)	32.0 (36.9%)	32.9 (44.4%)	Not applicable	Not applicable

1 NAT-GEFITINIB (gefitinib) 250 mg tablets (Natco Pharma (Canada) Inc.)
2 IRESSA® (gefitinib) 250 mg tablets (AstraZeneca Canada Inc.) were purchased in Canada.
3 Expressed as the median (range) only.
4 Expressed as the arithmetic mean (CV%) only.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

A standard program 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 gefitinib 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 feces 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 gefitinib 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) sensitiser. Results of an in vitro phototoxicity study demonstrated that gefitinib may have phototoxicity potential.

Acute Toxicity

Following a single oral dose of gefitinib 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 compri sed emesis, diarrhea, 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 gefitinib 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 feces were recorded in dogs, with no associated histopathological correlate. These changes were attributed to the pharmacological effects of gefitinib. 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 gefitinib. 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 gefitinib 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: 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 hemangiosarcomas 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.

Genotoxicity: Gefitinib 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 gefitinib.

Reproductive and Developmental Toxicology: There was, as expected from the pharmacological activity of gefitinib, a reduction in female fertility in the rat at a dose of 20 mg/kg/day. 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 gefitinib 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 gefitinib was administered to patients who are pregnant or are breast-feeding.

Pharmacokinetics – *In vivo*

Gefitinib 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.

Gefitinib 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. Gefitinib binds to both human serum albumin and α-1 acid glycoprotein.

Gefitinib was extensively metabolised 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. Gefitinib showed no enzyme induction potential in animals and no appreciable inhibition of human P450 isozymes. In vitro, gefitinib was predominantly metabolised by CYP3A4.

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

In rat and dog, gefitinib 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 gefitinib in animals and man are summarized below:

Table 8 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. IRESSA® Tablets, 250 mg, submission control 246584, Product Monograph, AstraZeneca Canada Inc., MAR 31, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr NAT-GEFITINIB

Gefitinib Tablets

Read this carefully before you start taking **NAT-GEFITINIB** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NAT-GEFITINIB**.

Serious Warnings and Precautions

- Only take NAT-GEFITINIB under the care of a health care professional who knows how to use anti-cancer drugs.
- NAT-GEFITINIB should not be used in patients with EGFR mutation negative tumours.
- NAT-GEFITINIB has not been studied in patients with serious kidney problems.
- NAT-GEFITINIB can cause the following side effects that can lead to death:
  - Liver failure.
  - Gastrointestinal perforation (a hole through the wall of the stomach or bowel).

What is NAT-GEFITINIB used for?

NAT-GEFITINIB is used in adults to treat a type of cancer called non-small cell lung cancer (NSCLC). NAT-GEFITINIB is used as your first treatment when your cancer:

- cannot be treated with other therapies or has spread from the lung to other parts of the body.
- has mutations (changes) in a gene called epidermal growth factor receptor tyrosine kinase (EGFR-TK).

A test is used to see if you have mutations in your EGFR-TK genes to determine whether NAT-GEFITINIB is right for you.

How does NAT-GEFITINIB work?

NAT-GEFITINIB works by binding to EGFR-TK mutations found on the surface of non-small cell lung cancer cells. This blocks the signalling from the EGFR-TK genes that are involved in the growth and spread of cancer cells. This may help to slow or stop your lung cancer from growing, or help to shrink the tumour.

What are the ingredients in NAT-GEFITINIB?

Medicinal ingredients: gefitinib

Non-medicinal ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone K-30, red iron oxide, sodium lauryl sulphate, talc, titanium dioxide, and yellow iron oxide.

NAT-GEFITINIB comes in the following dosage forms:

NAT-GEFITINIB is an oral tablet and each tablet contains 250 mg gefitinib.

Do not use NAT-GEFITINIB if:

- You are allergic to gefitinib or any of the other ingredients of NAT-GEFITINIB or the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NAT-GEFITINIB. Talk about any health conditions or problems you may have, including if you:

- have, or have had, lung diseases other than lung cancer. Some of them may worsen during treatment with NAT-GEFITINIB.
- have a history of stomach, intestine, or bowel problems.
- smoke.
- are at an increased age.
- are taking steroids or non-steroidal anti-inflammatory drugs (NSAIDS).
- have cancer that has spread to the bowel.
- are pregnant, or plan to become pregnant.
- are breastfeeding.
- have liver problems.
- have kidney problems.
- have eye problems, had eye surgery or wear contact lenses.
- have an intolerance to lactose.

Other warnings you should know about:

- **Bleeding problems:** Bleeding has been reported with the use of gefitinib. Bleeding problems include nosebleeds, blood in the urine, coughing up of blood and bleeding from the lungs.

- **Gastrointestinal (stomach, intestine or bowel) problems:** Serious or constant diarrhea, nausea, vomiting and weight loss eating disorders can occur. This might lead to dehydration. Tell your healthcare professional right away if you have these symptoms. If untreated, dehydration may lead to kidney problems.

- **Liver problems:** Liver problems, such as liver failure, hepatitis (liver inflammation) and cirrhosis (liver scarring) have occurred in patients taking gefitinib, which may cause death. You will get blood tests while taking NAT-GEFITINIB. These blood tests will tell your healthcare professional how your liver is working.

- **Lung problems:** Lung problems, such as Interstitial lung disease (a disease that inflames or scars lung tissue) have occurred in patients taking gefitinib, which may cause death.

- **Skin problems:** Toxic epidermal necrolysis and Stevens Johnson syndrome (severe skin rashes) and erythema multiforme (allergic skin reaction) have occurred in patients taking gefitinib, which may cause death.

See the "Serious side effects and what to do about them" table, below, for more information on these and other serious side effects.

Pregnancy and breastfeeding:

- Avoid becoming pregnant while taking NAT-GEFITINIB. It may harm your unborn child or make you lose the pregnancy.

- Tell your healthcare professional right away if you become pregnant or think you are pregnant during treatment with NAT-GEFITINIB. They will discuss the risks with you.
- You should not breastfeed while taking NAT-GEFITINIB. It is not known if NAT-GEFITINIB passes into breast milk. Talk to your healthcare professional about the best way to feed your baby during this time.

Driving and using machines: NAT-GEFITINIB may make you feel weak. This may affect your ability to drive or use machines. Before driving or using machines, wait until you are feeling well again.

Pediatric Patients: NAT-GEFITINIB is not for use in patients 16 years of age or younger.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NAT-GEFITINIB:

- St John's Wort, used to treat depression.
- Rifampicin, a drug used to treat bacterial infections.
- Macrolide antibiotics used to treat infections, such as erythromycin or clarithromycin.
- Drugs to treat fungal infections, such as itraconazole and ketoconazole.
- Drugs used to treat HIV/AIDS (protease inhibitors).
- Drugs used to treat seizures, such as phenytoin, carbamazepine, barbiturates.
- Drugs used to treat stomach acid, such as ranitidine, cimetidine, proton-pump inhibitors.
- Warfarin, a drug used to treat blood clots.
- Chemotherapy drugs such as vinorelbine.
- Grapefruit juice.

How to take NAT-GEFITINIB:

- Take NAT-GEFITINIB exactly as your healthcare professional tells you. Do not change your dose or stop taking NAT-GEFITINIB unless your healthcare professional tells you.
- Take your dose with or without food.

Usual dose:

Take one 250 mg tablet once daily, at about the same time each day.

Overdose:

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

Missed Dose:

- If there is at least 12 hours before the next dose, take the missed dose as soon as you remember. Take the next dose at your regular time.
- If there is less than 12 hours to the next dose, skip the missed dose. Wait until the regular time for your next dose.

- Do not take a double dose to make up for a missed dose.

What are possible side effects from using NAT-GEFITINIB?

These are not all the possible side effects you may feel when taking NAT-GEFITINIB. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Diarrhea
- Nausea, vomiting
- Loss of appetite
- Red and sore mouth (stomatitis)
- Dry mouth
- Cough
- Dehydration
- Skin reactions like rash, acne, itching dry and/or cracked skin
- Dry, itchy red eyes
- Weakness, tiredness
- Hair loss
- Fever
- Nosebleeds
- Nail problems
- Burning sensations during urination and frequency, urgent need to urinate

NAT-GEFITINIB can cause abnormal urine and blood test results. Your healthcare professional might do some tests before, during and after your treatment. They will tell you if your test results are abnormal and if you need treatment.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Gastrointestinal problems: Severe diarrhea, vomiting, nausea (feeling sick), eating disorders like anorexia, dehydration, thirst, loss of appetite, decreased urine.		√	
COMMON			
Allergic reactions: hives or rash, swelling of the face, lips, tongue or throat.		√	
Bleeding problems: coughing up blood, nosebleeds, bloody urine.		√	
Conjunctivitis (eye infection), blepharitis (inflamed eyelids) and dry eyes: blurred vision, increased sensitivity of the eyes to light, red and itchy eye, red and sore eyelids,		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
eye irritation.			
Lung problems, such as interstitial lung disease (diseases that inflame or scar lung tissue)**:** shortness of breath when rest (gets worse with exertion) with or without dry cough, fever.			√
UNCOMMON			
Corneal erosion (damaged outer layer of the eye) and Keratitis (inflamed eye): blurred or change in vision, new eye problems, such as pain, redness, watery eyes, increased sensitivity of eyes to light, eye ulcers with or without abnormal eyelash growth.		√	
Gastrointestinal perforation (a hole through the wall of the stomach or bowels): severe abdominal pain and tenderness, nausea, vomiting, chills or fever.			√
Liver problems, such as inflammation of the liver or liver failure: general feeling of being unwell, nausea, vomiting, with or without yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, unusual dark urine, unusual tiredness, bleeding easily, swollen abdomen.			√
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid pulse, nausea, vomiting.		√	
RARE			
Cutaneous vasculitis (inflammation of the blood vessels in the skin): bruising or patches of non-blanching rash on the skin.		√	
Erythema multiforme (an allergic skin reaction): raised red or purple skin patches, possibly with blister or crust in the centre with or without			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
mild itching or burning, peeling of the skin; possibly swollen lips.			
Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (severe skin rash): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands.			√
Hemorrhagic cystitis (inflammation of bladder): Burning sensation when passing urine and frequency, urgent need to urinate with blood in the urine.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk your healthcare professional.

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 at 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.

Storage:

- Keep out of 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.

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 Patient Medication 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.

This leaflet was prepared by Natco Pharma (Canada) Inc., Mississauga, Ontario, L5N 1P7.

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