GIOTRIF®

Afatinib (as afatinib dimaleate)

NAME OF THE MEDICINE

Active ingredient: afatinib (as afatinib dimaleate)

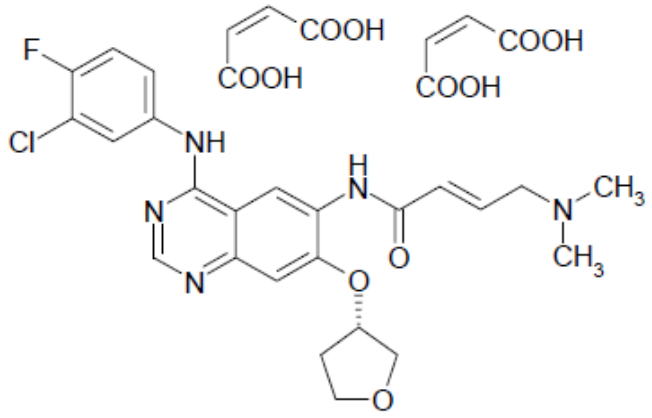
Chemical name: 2-butenamide, N-[4-[3(-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-,(2E)-, (2Z)-2-butenedioate (1:2)

Molecular formula: $C_{24}H_{25}ClFN_5O_3$ x 2 $C_4H_4O_4$ or $C_{32}H_{33}ClFN_5O_{11}$

CAS number: 850140-73-7 (salt form)
850140-72-6 (free base)

Molecular weight: 718.1 g/mol (salt form)
485.9 g/mol (free base)

Structural formula:



DESCRIPTION

Afatinib dimaleate is a white to brownish yellow powder. It is highly soluble in water and in aqueous buffer media up to pH 6 (> 50 mg/mL). Between pH 6 and 7, the solubility in these media decreases significantly but still exceeds 1 mg/mL. Above pH 7, solubility is reduced further to the low solubility of its free base (0.04 mg/mL at pH > 8). The highest solubility in organic solvents is observed for DMSO (> 50 mg/mL). Solubility in methanol is between 10 and 25 mg/mL; in 1:1 mixtures of acetonitrile, methanol, and ethanol with water the solubility exceeds 50 mg/mL. Dissociation constants: pKa1 = 8.2 ± 0.1; pKa2 = 5.0 ± 0.1. Partition coefficient: log P = 4.7 (at pH ≥ 9); log D = 3.8 (at pH 7.4).

GIOTRIF are film-coated tablets for oral administration containing 20 mg, or 30 mg, or 40 mg, or 50 mg afatinib (as afatinib dimaleate).

In addition, each GIOTRIF tablet contains:

Tablet Core: lactose, cellulose - microcrystalline, silica - colloidal anhydrous, crospovidone, magnesium stearate.

Film coating: hypromellose, macrogol 400, titanium dioxide, talc - purified, polysorbate 80, Colourant containing indigo carmine aluminium lake (only used for 50 mg, 40 mg and 30 mg tablets).

PHARMACOLOGY

Pharmacotherapeutic group: other antineoplastic agents – protein kinase inhibitors, ATC code: L01XE13.

Pharmacodynamics

Mechanism of action

Afatinib is an irreversible ErbB Family Blocker. Afatinib covalently binds to and irreversibly blocks signalling from all homo- and heterodimers formed by the ErbB family members EGFR (epidermal growth factor receptor, ErbB1), HER2 (human epidermal growth factor receptor 2, ErbB2), ErbB3 and ErbB4.

Pharmacodynamic effects

Aberrant ErbB signalling triggered by, for instance, EGFR mutations and/or amplification, HER2 amplification or mutation and/or ErbB ligand overexpression contributes to the malignant phenotype in subsets of patients across multiple cancer types.

In preclinical disease models with ErbB pathway deregulation, afatinib as a single agent effectively blocks ErbB receptor signalling resulting in tumour growth inhibition or tumour regression. Non-small cell lung cancer (NSCLC) models with either L858R or Del 19 EGFR mutations are particularly sensitive to afatinib treatment. Afatinib retains significant anti-tumour activity towards NSCLC cell lines *in vitro* and tumour models *in vivo* (xenografts or transgenic models) driven by mutant EGFR isoforms known to be resistant to the reversible EGFR inhibitors erlotinib and gefitinib such as T790M, although the activity of afatinib was significantly less than against non-resistant models.

Cardiac Electrophysiology

GIOTRIF at doses of 50 mg daily did not result in significant prolongation of the QTcF interval after single and multiple administrations in patients with relapsed or refractory solid tumours. There were no cardiac safety findings of clinical concern suggesting that GIOTRIF does not have a relevant effect on the QTcF interval.

Pharmacokinetics

Absorption

Following oral administration of GIOTRIF, maximum concentrations (C_{max}) of afatinib are observed approximately 2 to 5 hours post-dose. Mean C_{max} and $AUC_{0-\infty}$ values increased slightly more than proportional in the dose range from 20 mg to 50 mg GIOTRIF. Systemic exposure to afatinib is decreased by 50% (C_{max}) and 39% ($AUC_{0-\infty}$), when administered with a high-fat meal compared with administration in the fasted state. Based on population pharmacokinetic data derived from clinical trials in various tumour types, an average decrease of 26% in $AUC_{\tau,ss}$ was observed when food was consumed within 3 hours before or 1 hour after taking GIOTRIF. Therefore, food should not be consumed for at least 3 hours before and at least 1 hour after taking GIOTRIF (see DOSAGE AND ADMINISTRATION and PRECAUTIONS). After administration of GIOTRIF, the mean relative bioavailability was 92% (adjusted gMean ratio of $AUC_{0-\infty}$) when compared to an oral solution. The absolute bioavailability of afatinib has not been determined.

Distribution

In vitro binding of afatinib to human plasma proteins is approximately 95%.

Metabolism

Enzyme-catalysed reactions play a minor role in the metabolism of afatinib *in vivo*. Covalent adducts to proteins are the major circulating metabolites of afatinib. Approximately 2% of the afatinib dose was metabolised by FMO3 and the CYP3A4-dependent N-demethylation was too low to be quantitatively detected.

Excretion

Following administration of an oral solution of 15 mg afatinib, 85.4% of the dose was recovered in the faeces and 4.3% in urine. The parent compound afatinib accounted for 88% of the recovered dose. The apparent terminal half-life is 37 hours. Steady state plasma concentrations of afatinib are achieved within 8 days of multiple dosing of afatinib resulting in an accumulation of 2.77-fold (AUC) and 2.11-fold (C_{max}).

Renal impairment

Less than 5% of a single dose of afatinib is excreted via the kidneys. The safety, pharmacokinetics and efficacy of GIOTRIF have not been studied specifically in patients with renal impairment. Based on population pharmacokinetic data derived from clinical trials in various tumour types, no dose adjustments appear necessary in patients with mild or moderate renal impairment (see Population pharmacokinetic analysis in special populations below, and DOSAGE AND ADMINISTRATION).

Hepatic impairment

Afatinib is eliminated mainly by biliary/faecal excretion. Subjects with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment had similar exposure in comparison to healthy volunteers following a single dose of 50 mg GIOTRIF. This is consistent with population pharmacokinetic data derived from clinical trials in various tumour types (see Population pharmacokinetic analysis in special populations below). No starting dose adjustments appear necessary in patients with mild or moderate hepatic impairment (see DOSAGE AND ADMINISTRATION). The pharmacokinetics of afatinib had not been studied in subjects with severe (Child Pugh C) hepatic dysfunction (see PRECAUTIONS).

Population pharmacokinetic analysis in special populations

A population pharmacokinetic analysis was performed in 927 cancer patients (764 with NSCLC) receiving GIOTRIF monotherapy. No starting dose adjustment is considered necessary for any of the following covariates tested.

Age

No significant impact of age (range: 28-87 years) on the pharmacokinetics of afatinib could be observed.

Body weight

Plasma exposure ($AUC_{\tau,ss}$) was increased by 26% for a 42 kg patient (2.5th percentile) and decreased by 22% for a 95 kg patient (97.5th percentile) relative to a patient weighing 62 kg (median body weight of patients in the overall patient population).

Gender

Female patients had a 15% higher plasma exposure ($AUC_{\tau,ss}$, body weight corrected) than male patients.

Race

There was no statistically significant difference in afatinib pharmacokinetics between Asian and Caucasian patients. Also no obvious difference in pharmacokinetics for American Indian/Alaska native or Black patients could be detected based on the limited data available in these populations (6 and 9 out of 927 patients included in the analysis, respectively).

Renal impairment

Exposure to GIOTRIF moderately increased with lowering the creatinine clearance (CrCL), i.e. for a patient with a CrCL of 60 or 30 mL/min exposure ($AUC_{\tau,ss}$) to afatinib increased by 13% and 42%, respectively, and decreased by 6% and 20% for a patient with CrCL of 90 or 120 mL/min, respectively, compared to a patient with the CrCL of 79 mL/min (median CrCL of patients in the overall patient population analysed).

Hepatic impairment

Patients with mild and moderate hepatic impairment as identified by abnormal liver tests did not correlate with any significant change in afatinib exposure.

Other patient characteristics/intrinsic factors

Other patient characteristics/intrinsic factors found with a significant impact on afatinib exposure were: ECOG performance score, lactate dehydrogenase levels, alkaline phosphatase levels and total protein. The individual effect sizes of these covariates were considered not clinically relevant.

Smoking history, alcohol consumption, or presence of liver metastases had no significant impact on the pharmacokinetics of afatinib.

Pharmacokinetic Drug Interactions

Drug Transporters:

P-glycoprotein (P-gp)

Effect of P-gp inhibitors and inducers on afatinib

Two trials were conducted to assess the effect of ritonavir, a potent inhibitor of P-gp, on the pharmacokinetics of afatinib. In one trial, the relative bioavailability of afatinib was investigated when ritonavir (200 mg b.i.d. for 3 days) was given either simultaneously or 6 hours after a single dose of 40 mg GIOTRIF. The relative bioavailability of afatinib was 119% ($AUC_{0-\infty}$) and 104% (C_{max}) when administered simultaneously with ritonavir and 111% ($AUC_{0-\infty}$) and 105% (C_{max}) when ritonavir was administered 6 hours after GIOTRIF. In a second trial, when ritonavir (200 mg b.i.d. for 3 days) was administered 1 hour before a single dose of 20 mg GIOTRIF, exposure to afatinib increased by 48% ($AUC_{0-\infty}$) and 39% (C_{max}) (see PRECAUTIONS, INTERACTIONS WITH OTHER MEDICINES and DOSAGE AND ADMINISTRATION).

Pre-treatment with rifampicin (600 mg q.d. for 7 days), a potent inducer of P-gp, decreased the plasma exposure to afatinib by 34% ($AUC_{0-\infty}$) and 22% (C_{max}) after administration of a single dose of 40 mg GIOTRIF (see PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES).

Effect of afatinib on P-gp Substrates

Based on *in vitro* data, afatinib is a moderate inhibitor of P-gp. However, based on clinical data it is considered unlikely that GIOTRIF treatment will result in changes of the plasma concentrations of other P-gp substrates.

Breast cancer resistance protein (BCRP)

In vitro studies indicated that afatinib is a substrate and an inhibitor of the transporter BCRP.

Drug Uptake Transport Systems

In vitro data indicated that drug-drug interactions with afatinib due to inhibition of OATB1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, and OCT3 transporters are considered unlikely.

Drug Metabolising Enzymes:

Cytochrome P450 (CYP) enzymes

Effect of CYP enzymes inducers and inhibitors on afatinib

In vitro data indicated that drug-drug interactions with afatinib due to inhibition or induction of CYP enzymes by concomitant medicines are considered unlikely. In humans it was found that enzyme-catalysed metabolic reactions play a negligible role in the metabolism of afatinib. Approximately 2% of the afatinib dose was metabolised by FMO3 and the CYP3A4-dependent N-demethylation was too low to be quantitatively detected.

Effect of afatinib on CYP enzymes

Afatinib is neither an inhibitor or an inducer of CYP enzymes. Therefore, GIOTRIF is unlikely to affect the metabolism of other medicines that are dependent on CYP enzymes.

UDP-glucuronosyltransferase 1A1 (UGT1A1)

In vitro data indicated that drug-drug interactions with afatinib due to inhibition of UGT1A1 are considered unlikely.

CLINICAL TRIALS

Non-Small Cell Lung Cancer (NSCLC)

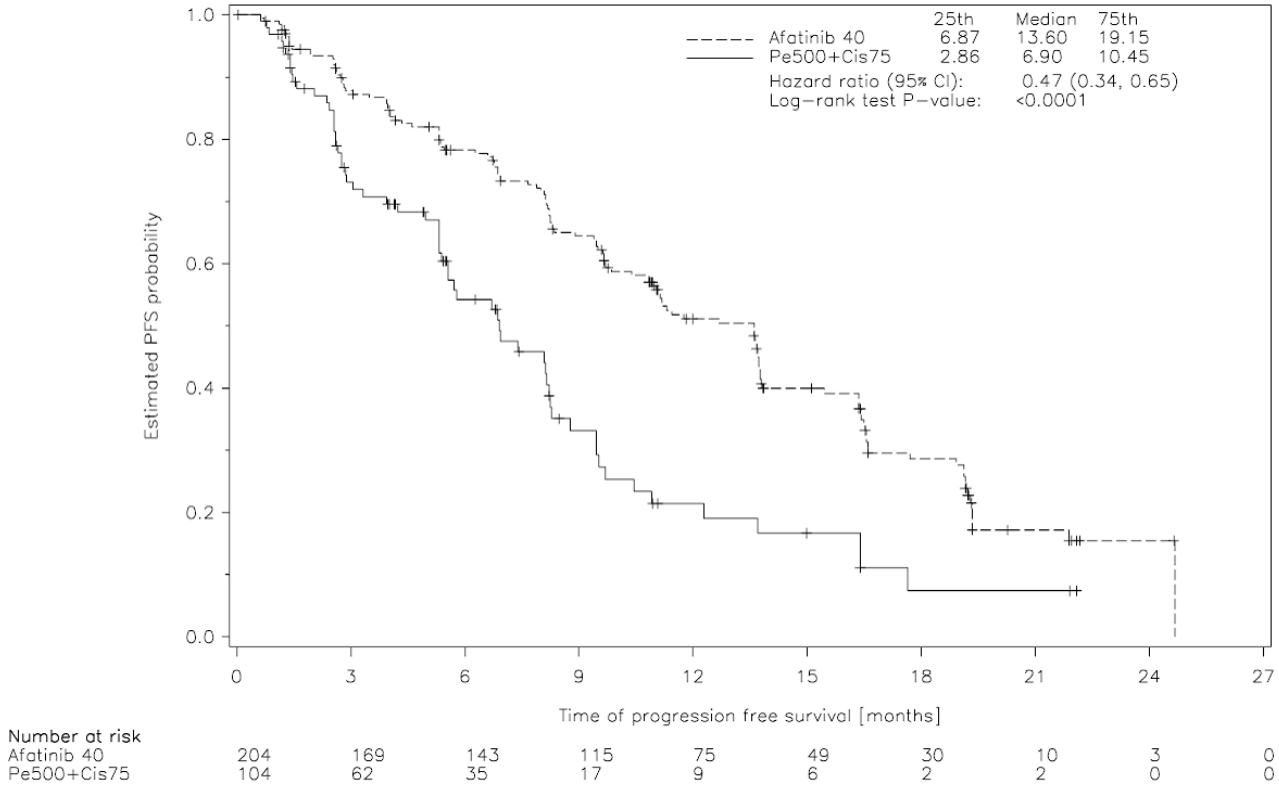
LUX-Lung 3 (1200.32)

In the first-line setting, the efficacy and safety of GIOTRIF in patients with EGFR mutation-positive locally advanced or metastatic NSCLC (stage IIIB or IV) were assessed in a global, randomised, multicentre, open-label trial (LUX-Lung 3). Patients naïve to prior systemic treatment for their advanced or metastatic disease were screened for the presence of 29 different EGFR mutations using a polymerase chain reaction (PCR)-based method (TheraScreen®: EGFR29 Mutation Kit, Qiagen Manchester Ltd). Patients (N=345) were randomised (2:1) to receive GIOTRIF 40 mg orally once daily (N=230) or up to 6 cycles pemetrexed/cisplatin (N=115). Randomisation was stratified according to EGFR mutation status (L858R; Del 19; other) and race (Asian; non-Asian). Dose escalation of GIOTRIF to 50 mg was allowed after 21 days on treatment in case of no or limited drug-related adverse events (i.e. absence of diarrhoea, skin rash, stomatitis, and/or other drug-related events above Common Terminology Criteria for Adverse Events [CTCAE] Grade 1), compliant dosing of GIOTRIF and no prior dose reduction.

In the overall trial population, the primary endpoint of progression free survival (PFS – independent review, 221 events) showed a statistically significant improvement in the median PFS between patients treated with GIOTRIF and patients treated with chemotherapy (11.1 vs. 6.9 months HR 0.58, 95% CI 0.43-0.78; p=0.0004). The percentage of patients alive and without progression (PFS rate) at 12 months was 46.5% in patients treated with GIOTRIF and 22% in patients treated with chemotherapy for the overall trial population.

In the pre-defined sub-group of common mutations (L858R, Del 19) for GIOTRIF (N=204) and chemotherapy (N=104) the median PFS was 13.6 months vs. 6.9 months respectively (HR 0.47; 95% CI 0.34-0.65; p<0.0001). The PFS rate at 12 months was 51.1% in patients treated with GIOTRIF and 21.4% in patients treated with chemotherapy. The Kaplan-Meier curve for PFS analysis in common mutations is shown in Figure 1.

Figure 1: Kaplan-Meier Curve for PFS by independent review by treatment group in LUX-Lung 3 for sub-group of common mutations (L858R, Del 19)



The subgroup of “other” (uncommon) mutations was small (N=37; 11%) and genetically heterogeneous (10 different molecular subtypes with unequal distribution between the treatment groups) thereby limiting the value and interpretation of the pooled statistical analyses in this subset. Of the 26 GIOTRIF-treated patients, eight achieved a partial response (N=4) or prolonged disease control of longer than 6 months (N=4): 4 patients with mutations of the category L858R+T790M (1 PR, PFS 11.0 months; 3 SD, 9.6+, 8.3, and 6.7 months); and 1 patient in each with a mutation of the categories L861Q (1 SD, 8.3 months); G719X (1 PR, 10.8 months); S768I+L858R (1 PR, 13.8+ months); and S768I (1 PR, 19.2+ months). The PFS was shorter than 6 months in all patients with the following mutation categories: T790M alone (N=2), deletion 19 and T790M (N=3), G719X and T790M (N=1), exon 20 insertion (n=6). There were 11 chemotherapy-treated patients in the “other” uncommon EGFR mutation subgroup; of these, four (36%) achieved a partial response.

Efficacy results of trial LUX-Lung 3 are summarised in Table 1 below.

Table 1: Efficacy results of GIOTRIF vs. pemetrexed/cisplatin (LUX-Lung 3) based on primary analysis as of 9 February 2012 (Independent review)

	GIOTRIF (N=230)	**Pemetrexed / Cisplatin** (N=115)	**Hazard Ratio (HR) / Odds Ratio (OR) (95% CI) p-value**
PFS, Overall Study Population			
Months (median)	**11.1**	**6.9**	HR 0.58 (0.43-0.78) 0.0004
1-year PFS Rate	46.5%	22.0%	
18-month PFS Rate	26.4%	8.6%	
PFS, Patients with L858R or Del 19 Mutations[1]			
Months (median)	**13.6**	**6.9**	HR 0.47 (0.34-0.65) <0.0001
1-year PFS Rate	51.1%	21.4%	
18-month PFS Rate	28.6%	7.4%	
Objective Response Rate (CR+PR) [2]	**56.1%**	**22.6%**	OR 4.66 (2.77-7.83) <0.0001
Disease Control Rate (CR+PR+SD) [2]	**90.0%**	**80.9%**	OR 2.14 (1.13-4.04) 0.0189
Response Duration			
Months (median)	**11.1**	**5.5**	-
Overall Survival (OS), Overall Trial Population			
Months (median) [3]	**28.2**	**28.2**	HR 0.88 (0.66, 1.17) 0.39

[1] N=308 (GIOTRIF: 204, pemetrexed/cisplatin: 104)
[2] CR=complete response; PR=partial response; SD=stable disease
[3] OS analysis as of December 2013

The effect on PFS was consistent within major subgroups, including gender, age, race, ECOG status, and mutation type (L858R, Del 19). In the pre-defined sub-group of common mutations (L858R, Del 19) for GIOTRIF (N=203) and chemotherapy (N=104) the median OS was 31.6 months vs. 28.2 months (HR=0.78, 95% CI (0.58, 1.06), p=0.1090).

PFS benefit was accompanied by improvement in disease-related symptoms, as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ-C30 and QLQ-LC13). In the overall trial population, GIOTRIF significantly delayed the time to deterioration for pre-specified symptoms of cough (HR 0.6; p=0.0072; median time not reached for GIOTRIF vs. 8.0 months for chemotherapy) and dyspnoea (HR 0.68; p=0.0145; median time of 10.3 vs. 2.9 months). Significantly more patients treated with GIOTRIF compared with those treated with chemotherapy had improvement for dyspnoea (64% vs. 50%; p=0.0103) and individual items of pain ('Have pain': 56.0% vs. 40.0%; p=0.0095; 'Pain in chest': 51.0% vs. 37.0%; p=0.0184; 'Pain in arm or shoulder': 41.0% vs. 26.0%; p=0.0103). For cough, numerically more patients improved on GIOTRIF (67% vs. 60%; p=0.2444).

<u>LUX-Lung 2 (1200.22)</u>

LUX-Lung 2 was an open label single arm Phase II trial which investigated the efficacy and safety of GIOTRIF in 129 EGFR TKI-naïve patients with locally advanced or metastatic lung adenocarcinoma (stage IIIB or IV) with EGFR mutations. Patients were enrolled in the first-line (N=61) or second-line setting (N=68) (i.e. after failure of one prior chemotherapy regimen).

Patients were centrally screened for EGFR mutations. Patients received either 40 mg (N=30) or 50 mg (N=99) of GIOTRIF once daily.

The primary endpoint was ORR. Secondary endpoints included PFS, DCR and OS.

In 61 patients treated in the first-line setting, confirmed ORR was 65.6% and DCR was 86.9% according to independent review. The median PFS was 12.0 months by independent review and 15.6 months by investigator assessment. Median OS was not reached in the first-line population. Efficacy was similarly high in the group of patients who had received prior chemotherapy (N=68; ORR 57.4%; PFS by independent review 8 months and by investigator assessment 10.5 months; DCR 77.9%). Median OS in the second line patients was 23.3 months (95% CI 18.5-38).

INDICATIONS

GIOTRIF is indicated as monotherapy for the treatment of patients with advanced or metastatic non-squamous non-small cell carcinoma of the lung, either as first line therapy or after failure of cytotoxic chemotherapy. Tumours must have Epidermal Growth Factor Receptor (EGFR) exon 19 deletions or L858R substitution mutations.

CONTRAINDICATIONS

GIOTRIF is contraindicated in patients with known hypersensitivity to afatinib or to any of the excipients.

PRECAUTIONS

Assessment of EGFR mutation status

When assessing the EGFR mutation status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

Diarrhoea

Diarrhoea, including severe diarrhoea, has been reported during treatment with GIOTRIF (see ADVERSE EFFECTS). Diarrhoea may result in electrolyte abnormalities and/or dehydration with or without renal impairment, which in rare cases has resulted in fatal outcomes. Monitoring for serum electrolyte abnormalities may be required depending on the severity and duration of diarrhoea. Diarrhoea usually occurred within the first 2 weeks of treatment. Grade 3 diarrhoea most frequently occurred within the first 6 weeks of treatment. Proactive management of diarrhoea including adequate hydration combined with antidiarrhoeal agents especially within the first six weeks of the treatment is important and should start at first signs of diarrhoea. Antidiarrhoeal agents (e.g. loperamide) should be used and if necessary their dose should be escalated to the highest recommended approved dose. Antidiarrhoeal agents should be readily available to the patients so that treatment can be initiated at first signs of diarrhoea and continued until loose bowel movements cease for 12 hours. Patients with severe diarrhoea may require interruption and dose reduction or discontinuation of therapy with GIOTRIF (see DOSAGE AND ADMINISTRATION). Patients who become dehydrated may require administration of intravenous electrolytes and fluids.

Skin related adverse events

Rash/acne has been reported in patients treated with GIOTRIF (see ADVERSE EFFECTS). In general, rash manifests as a mild or moderate erythematous and acneiform rash, which may occur or worsen in areas exposed to sun. For patients who are exposed to sun, protective clothing, and/or use of sun screen is advisable. Early intervention (e.g. emollients, antibiotics) of dermatologic reactions can facilitate continuous GIOTRIF treatment.

Patients with prolonged or severe skin reactions may also require temporary interruption of therapy, dose reduction (see DOSAGE AND ADMINISTRATION), additional therapeutic intervention, and referral to a specialist with expertise in managing these dermatologic effects. Bullous, blistering and exfoliative skin conditions have been reported including rare cases suggestive of Stevens-Johnson syndrome. GIOTRIF treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

Female gender, lower body weight and underlying renal impairment

Higher exposure to afatinib has been observed in female patients, patients with lower body weight and those with underlying renal impairment (see PHARMACOLOGY, Pharmacokinetics). This could result in a higher risk of developing EGFR-mediated adverse events such as diarrhoea, rash/acne and stomatitis. Closer monitoring is recommended in patients with these risk factors.

Interstitial Lung Disease (ILD)

There have been reports of ILD or ILD-like events (such as Lung infiltration, Pneumonitis, Acute Respiratory Distress Syndrome, Alveolitis allergic), including fatalities, in patients receiving GIOTRIF for treatment of NSCLC. Drug-related ILD-like events were reported in 0.7% of more than 3800 patients treated. CTCAE Grade ≥ 3 ILD-like events, regardless of causality, were reported in 1% of patients (see ADVERSE EFFECTS). Patients with a history of ILD have not been studied. Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD. GIOTRIF should be interrupted pending investigation of these symptoms. If ILD is diagnosed, GIOTRIF should be permanently discontinued and appropriate treatment instituted as necessary (see DOSAGE AND ADMINISTRATION).

Severe hepatic impairment

Hepatic failure, including fatalities, has been reported during treatment with GIOTRIF in less than 1% of patients. In these patients, confounding factors have included pre-existing liver disease and/or co-morbidities associated with progression of underlying malignancy. Periodic liver function testing is recommended in patients with pre-existing liver disease. GIOTRIF dose interruption may become necessary in patients who experience worsening of liver function (see DOSAGE AND ADMINISTRATION). In patients who develop severe hepatic impairment while taking GIOTRIF, treatment should be discontinued.

Keratitis

Symptoms such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with GIOTRIF should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. GIOTRIF should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration (see ADVERSE EFFECTS).

Left ventricular function

Left ventricular dysfunction has been associated with HER2 inhibition. GIOTRIF has not been studied in patients with abnormal left ventricular ejection fraction (LVEF) or those with significant cardiac history. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during GIOTRIF treatment, should be considered. In patients that develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

In patients with an ejection fraction below the institution's lower limit of normal, cardiac consultation as well as GIOTRIF treatment interruption or discontinuation should be considered.

Pancreatitis

Adverse events of pancreatitis have been observed uncommonly in patients treated with GIOTRIF. Although a causal association was not established, patients who develop symptoms consistent with the diagnosis should be evaluated for pancreatitis.

P-glycoprotein (P-gp) interactions

Concomitant treatment with strong inducers of P-gp may decrease exposure to afatinib (see DOSAGE AND ADMINISTRATION, and INTERACTIONS WITH OTHER MEDICINES).

Combination with vinorelbine in HER2 positive metastatic breast cancer

An early interim overall survival analysis of a randomised Phase III trial in HER2 positive metastatic breast cancer showed an increased mortality in patients receiving GIOTRIF in combination with vinorelbine compared to trastuzumab and vinorelbine. The combination of GIOTRIF and vinorelbine was also associated with a higher rate of adverse events (such as diarrhoea, rash) and fatal events related to infections and cancer progression. GIOTRIF combined with vinorelbine should not be used in patients with HER2 positive metastatic breast cancer.

Lactose

GIOTRIF contains lactose. Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive or operate machinery have been performed.

Effects on fertility

Fertility studies in humans have not been performed with GIOTRIF. Available nonclinical toxicology data have shown effects on reproductive organs at higher doses. Therefore, an adverse effect of GIOTRIF therapy on human fertility cannot be excluded.

A fertility study in male and female rats by the oral route up to the maximum tolerated dose revealed no significant impact on fertility. Post-implantation loss was increased at the highest dose. The systemic exposure (AUC_{0-24}) achieved in male and female rats was similar to or less than that observed in patients (1.3 times and 0.51 times, respectively).

Use in pregnancy (Category C)

Based on the mechanism of action, GIOTRIF has the potential to cause fetal harm. The embryo-fetal development studies in rats and rabbits on afatinib revealed no indication of teratogenicity up to dose levels (16 mg/kg/day in rats and 10 mg/kg/day in rabbits) including maternal death. However, afatinib showed very limited placental transfer in rats. Changes identified were reduced fetal weights (rat and rabbit), abortions (rabbit), and skeletal alterations (flexure of extremities, abnormal rib curvature, lumbar ribs) and dermal variation (less integument of forelimbs) (rabbit). The systemic exposures (AUC), achieved in these experiments were either slightly above (2.2 times in rats) or below (0.3 times in rabbits) the exposure in patients.

There are no studies in pregnant women using GIOTRIF. It is unknown whether afatinib crosses the placenta in humans. Therefore, the potential risk for humans is thus unknown.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with GIOTRIF. Adequate contraceptive methods should be used during therapy and for at least 2 weeks after the last dose. If GIOTRIF is used during pregnancy or if the patient becomes pregnant while receiving GIOTRIF, the patient should be apprised of the potential hazard to the fetus.

Use in lactation

Radiolabelled afatinib administered orally to lactating rats was excreted into milk. The average concentrations in milk at time points 1 h and 6 h post dose were approximately 80- and 150-fold above the respective concentration in plasma.

Based on nonclinical data it is likely that afatinib is excreted in human milk. A risk to the nursing child cannot be excluded. Mothers should be advised against breast-feeding while receiving GIOTRIF.

A study in rats by the oral route up to the maximum tolerated dose revealed no significant impact on the attainment of developmental landmarks, sexual maturation or performance by behavioural assessments. Effects were limited to lower birth weight and body weight gain of offspring. The highest total systemic exposure (AUC_{0-24}) achieved in female rats was less than that observed in patients (0.23 times).

Genotoxicity

Afatinib was weakly positive in one bacterial strain in a (Ames) mutagenicity assay and induced chromosome aberrations in human lymphocytes *in vitro* at a cytotoxic concentration. However, testing in the Muta™ Mouse *in vivo* mutagenicity assay at oral doses up to 47 mg/kg for 4 weeks, in the rat bone marrow micronucleus assays at up to 32 mg/kg/day for 2 weeks and 18 mg/kg/day for 4 weeks (7 and 4 times, respectively, the clinical exposure based on AUC), and in the Comet assay (detecting DNA damage) using cells from rats given two doses at 200 mg/kg, showed no evidence of genotoxicity.

The balance of evidence indicates that afatinib is unlikely to pose a genotoxic risk to patients.

Carcinogenicity

Carcinogenicity studies have not been conducted with GIOTRIF.

Phototoxicity

An *in vitro* mouse 3T3 cell phototoxicity test with afatinib was performed. It was concluded that GIOTRIF may have phototoxicity potential. See PRECAUTIONS, Skin related adverse events.

Food effect on afatinib

Co-administration of a high-fat meal with GIOTRIF resulted in a significant decrease of exposure to afatinib by about 50% in regard to C_{max} and 39% in regard to $AUC_{0-\infty}$. GIOTRIF should be administered without food (see PHARMACOLOGY, Pharmacokinetics and DOSAGE AND ADMINISTRATION).

INTERACTIONS WITH OTHER MEDICINES

P-glycoprotein (P-gp) interactions

Based on *in vitro* data, afatinib is a substrate of P-gp. Based on clinical data, concomitant administration of strong P-gp inhibitors or inducers may alter exposure to afatinib. Results of a drug interaction trial demonstrated that GIOTRIF can be safely combined with P-gp inhibitors (such as ritonavir) as long as the inhibitor is administered simultaneously with or after GIOTRIF. If administered prior to GIOTRIF, strong P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus,

nelfinavir, saquinavir, and amiodarone) may increase exposure to afatinib and should be used with caution. (see PHARMACOLOGY, Pharmacokinetics; PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Strong P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's Wort) may decrease exposure to afatinib (see PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS).

Interactions with breast cancer resistance protein (BCRP)

In vitro studies indicated that afatinib is a substrate and an inhibitor of the transporter BCRP. Afatinib may increase the bioavailability of orally administered BCRP substrates (including but not limited to rosuvastatin and sulfasalazine) and caution should be exercised when co-administrating GIOTRIF and BCRP substrates.

ADVERSE EFFECTS

The safety evaluation of GIOTRIF is based on the data from more than 3800 patients, including more than 1638 NSCLC patients treated with a daily dose of GIOTRIF 50 mg monotherapy and more than 497 NSCLC patients who received GIOTRIF 40 mg monotherapy once daily.

In the pivotal LUX-Lung 3 (1200.32) trial a total of 229 EGFR TKI naïve patients were treated with GIOTRIF with a starting dose of 40 mg once daily. A total of 111 patients were treated with pemetrexed/cisplatin. The overall incidence of Adverse Drug Reactions (ADRs) in patients treated with once daily GIOTRIF 40 mg was similar to pemetrexed/cisplatin (100% vs. 96%). The incidence of diarrhoea (95% vs. 15%) and rash/acne (89% vs. 6%) ADRs was higher in the GIOTRIF-treated patients than in those patients treated with pemetrexed/cisplatin, respectively. Dose reductions due to ADRs occurred in 57% of GIOTRIF-treated patients. Overall dose reduction led to a lower frequency of common adverse events (e.g. after first dose reduction, frequency for diarrhoea regardless of causality decreased from 96% to 52%).

Elderly patients may be more likely to experience a higher grade of the more frequent EGFR TKI-associated events. Grade 3 AEs were observed in 67% in patients ≥70 years of age versus 47% in patients <70 years of age.

Discontinuation of therapy due to ADRs was lower in patients who received once daily GIOTRIF 40 mg compared with pemetrexed/cisplatin (8% vs. 12%). In patients treated with GIOTRIF, discontinuation due to ADRs diarrhoea and rash/acne was 1.3% and 0%, respectively.

Very Common ADRs in GIOTRIF-treated patients occurring in at least 10% of patients in trial LUX-LUNG 3 are summarised by National Cancer Institute – Common Terminology Criteria (NCI-CTC) Grade in Table 2.

Table 2: Adverse Events Reported in ≥10% of GIOTRIF Treated Patients in LUX-Lung 3

	GIOTRIF N=229			**Pemetrexed/Cisplatin N=111**		
Adverse Event	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Gastrointestinal disorders						
Diarrhoea	96	15	0	23	2	0
Stomatitis[1]	71	8	0	15	1	0
Nausea	25	1	0	68	4	0
Vomiting	23	4	0	47	3	0
Constipation	13	0	0	35	0	0

	GIOTRIF N=229			Pemetrexed/Cisplatin N=111		
Adverse Event	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Cheilitis	12	0	0	1	0	0
Skin and subcutaneous tissue disorders						
Rash[2]	71	14	0	11	0	0
Dermatitis acneiform[3]	35	3	0	0	0	0
Pruritus[4]	21	0	0	1	0	0
Dry skin[5]	31	0	0	2	0	0
Alopecia	13	0	0	18	0	0
Infections and infestations						
Paronychia[6]	58	11	0	0	0	0
Nasopharyngitis	14	0	0	8	0	0
Cystitis[7]	13	1	0	5	0	0
Upper respiratory tract infection	11	0	0	4	0	0
Metabolism and nutrition disorders						
Decreased appetite	29	4	0	55	4	0
Hypokalemia[8]	11	2	2	5	3	1
General disorders and administration site conditions						
Fatigue	19	2	0	36	10	0
Pyrexia[10]	12	0	0	6	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	17	0	0	2	1	0
Cough	15	0	0	19	1	0
Rhinorrhea[9]	11	0	0	6	0	0
Investigations						
Weight decreased	17	1	0	14	1	0
Alanine aminotransferase increased	11	2	0	4	0	0
Psychiatric disorders						
Insomnia	15	0	0	9	0	0
Nervous system disorder						
Headache	14	0	0	17	0	0
Dizziness	11	0	0	11	0	0
Musculoskeletal and connective tissue disorders						
Back pain	14	0	0	12	2	0
Eye disorders						
Conjunctivitis[11]	11	0	0	3	0	0

[1]Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

[2]Includes group of rash preferred terms

[3]Includes acne, acne pustular, dermatitis acneiform

[4]Includes pruritus, pruritus generalized

[5]Includes dry skin, skin chapped

[6]Includes paronychia, nail infection, nail bed infection

[7]Includes cystitis, urinary tract infection

[8]Includes hypokalemia, blood potassium decreased

[9]Includes rhinorrhea, nasal inflammation

[10]Includes pyrexia, body temperature increased

[11]Includes conjunctivitis, conjunctival irritation, conjunctival hyperemia

Liver function test abnormalities (including elevated alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were observed in patients receiving GIOTRIF 40 mg. These elevations were mainly transient and did not lead to discontinuation of treatment. Grade 2 (> 2.5 to 5.0 times ULN [upper limit of normal]) ALT elevations occurred in 7.9% and 3.6% of patients treated with GIOTRIF or chemotherapy, respectively. Grade 3 (> 5.0 to 20.0 times ULN) elevations occurred in 3.5% and 1.8% of patients treated with GIOTRIF or chemotherapy, respectively (see PRECAUTIONS).

The safety of GIOTRIF monotherapy at starting doses of 40 mg or 50 mg once daily was assessed in pooled analyses of patients in all NSCLC trials. In general, the types of ADRs were generally associated with the EGFR inhibitory mode of action of afatinib. The ADR profile from the pooled analysis in NSCLC patients exposed to 40 mg GIOTRIF once daily was consistent with the LUX-Lung 3 trial. CTCAE Grade 1 or 2 ADRs occurred in 58.8% of patients treated with GIOTRIF 40 mg. The majority of ADRs were of CTCAE Grade 1 or 2 and manageable as described in sections DOSAGE AND ADMINISTRATION, and PRECAUTIONS. CTCAE Grade 3 or 4 ADRs occurred in 38% of patients treated with GIOTRIF 40 mg. CTCAE Grade 3 ADRs were also manageable as described in sections DOSAGE AND ADMINISTRATION, and PRECAUTIONS, which was reflected in the low treatment discontinuation rate of 7% due to ADRs.

A summary of common ADRs of diarrhoea and rash/acne in all patients receiving 40 mg/day GIOTRIF monotherapy in NSCLC studies is provided in Table 3.

Table 3: Pooled analyses of drug related diarrhoea and rash/acne in all patients receiving 40 mg/day GIOTRIF monotherapy in NSCLC studies

	EGFR TKI-naïve (Starting dose 40 mg/day) N=497
CTCAE[a] Grade 3 rash/acne	14.3%
CTCAE[a] Grade 3 diarrhoea	9.9%
Discontinuation due to rash/acne (all Grades)	1.2%
Discontinuation due to diarrhoea (all Grades)	0.6%

[a] NCI Common Terminology Criteria for Adverse Events v 3.0

One patient (0.2%) receiving a 40 mg starting dose experienced Grade 4 rash/acne.

The ADRs pooled from all NSCLC trials with daily GIOTRIF doses as monotherapy (N=2135) are shown below by system organ class. The frequency categories used are defined as:

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100)

Infections and infestations:
Very common: paronychia
Common: cystitis

Metabolism and nutrition disorders:
Very common: decreased appetite
Common: dehydration, hypokalemia

Nervous system disorders:
Common: dysgeusia

Eye disorders:
Common: conjunctivitis, dry eye
Uncommon: keratitis

Respiratory, thoracic and mediastinal disorders:
Very common: epistaxis
Common: rhinorrhoea
Uncommon: interstitial lung disease

Gastrointestinal disorders:
Very common: diarrhoea, stomatitis, nausea, vomiting
Common: dyspepsia, cheilitis
Uncommon: pancreatitis

Hepatobiliary disorders:
Common: ALT increased, AST increased

Skin and subcutaneous tissue disorders:
Very common: rash, dermatitis acneiform, pruritus, dry skin
Common: palmar-plantar erythrodysesthesia syndrome

Musculoskeletal and connective tissue disorders:
Common: muscle spasms

Renal and urinary disorders:
Common: renal impairment/renal failure

General disorders and administration site conditions:
Common: pyrexia

Investigations:
Common: weight decreased

DOSAGE AND ADMINISTRATION

Non-Small Cell Lung Cancer (NSCLC)

The recommended dose of GIOTRIF is 40 mg orally once daily for first-line treatment or for patients not previously treated with an EGFR Tyrosine Kinase Inhibitor (EGFR TKI-naïve patients).

GIOTRIF should be taken without food. Food should not be consumed for at least 3 hours before and at least 1 hour after taking GIOTRIF (see PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS). Tablets should be swallowed whole with water.

GIOTRIF treatment should be continued until disease progression or until no longer tolerated by the patient (see Table 4 below).

Dose escalation

A dose escalation to a maximum of 50 mg/day may be considered in EGFR TKI-naïve patients who tolerate a 40 mg/day dose (i.e. absence of diarrhoea, skin rash, stomatitis and other drug related events of CTCAE Grade > 1) in the first 3 weeks. The dose should not be escalated in patients with a prior dose reduction. The maximum daily dose in any setting is 50 mg.

Dose adjustment for adverse reactions

Symptomatic adverse drug reactions (e.g. severe/persistent diarrhoea or skin-related adverse reactions) may be successfully managed by treatment interruption and dose reductions of GIOTRIF as outlined in Table 4 (see ADVERSE EFFECTS; for further details on management of specific drug-related Adverse Events, see PRECAUTIONS).

Table 4: Dose Adjustment Information for Adverse Reactions

CTCAE[a] Drug Related Adverse Event	**Recommended Dosing of GIOTRIF**	
Grade 1 or Grade 2	No interruption[b]	No dose adjustment
Grade 2 (prolonged[c] or intolerable) or Grade ≥ 3	Interrupt until Grade 0/1[b]	Resume with dose reduction by 10 mg decrements[d]

[a] NCI Common Terminology Criteria for Adverse Events v 3.0
[b] In case of diarrhoea, antidiarrhoeal medicines (e.g. loperamide) should be taken immediately and continued for persistent diarrhoea until loose bowel movements cease.
[c] > 48 hours of diarrhoea and/or > 7 days of rash
[d] If patient cannot tolerate 20 mg/day, permanent discontinuation of GIOTRIF should be considered

Interstitial Lung Disease (ILD) should be considered if a patient develops acute or worsening of respiratory symptoms in which case GIOTRIF should be interrupted pending evaluation. If ILD is diagnosed, GIOTRIF should be discontinued and appropriate treatment instituted as necessary (see PRECAUTIONS).

Missed dose

If a dose of GIOTRIF is missed, it should be taken during the same day as soon as the patient remembers. However, if the next scheduled dose is due within 8 hours then the missed dose must be skipped.

Patients with renal impairment

The safety, pharmacokinetics and efficacy of GIOTRIF have not been studied in a dedicated trial in patients with renal impairment. Based on population pharmacokinetic analyses (see PHARMACOLOGY, Pharmacokinetics), adjustments to the starting dose are not necessary in patients with mild or moderate renal impairment. GIOTRIF treatment in patients with severely impaired renal function (< 30 mL/min creatinine clearance) is not recommended.

Patients with hepatic impairment

Exposure to afatinib is not significantly changed in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment (see PHARMACOLOGY, Pharmacokinetics). Adjustments to the starting dose are not necessary in patients with mild or moderate hepatic impairment. GIOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. GIOTRIF treatment in this population is not recommended.

Age, Race, Gender

No dose adjustment is necessary based on patient age, race, or gender (see PHARMACOLOGY, Pharmacokinetics).

Paediatric population

The safety and efficacy of GIOTRIF have not been studied in paediatric patients. Therefore, treatment of children or adolescents with GIOTRIF is not recommended.

Use of P-glycoprotein (P-gp) inhibitors

If P-gp inhibitors need to be taken, they should be administered simultaneously with or after GIOTRIF (see PHARMACOLOGY, Pharmacokinetics; PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES).

Alternative method of administration

If dosing of whole tablets is not possible, GIOTRIF tablets can be dispersed in approximately 100 mL of noncarbonated drinking water. No other liquids should be used. The tablet should be dropped into the water without crushing it, and stirred occasionally for up to 15 minutes until the tablet is broken up into very small particles. The dispersion should be consumed immediately. The glass should be rinsed with approximately 100 mL of water which should also be consumed. The dispersion can also be administered through a gastric tube.

OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

Symptoms

The highest dose of GIOTRIF studied in a limited number of patients in Phase I clinical trials was 160 mg once daily for 3 days and 100 mg once daily for 2 weeks. The adverse reactions observed at this dose were primarily dermatological (rash/acne) and gastrointestinal events (especially diarrhoea). Overdose in 2 healthy adolescents involving the ingestion of 360 mg each of GIOTRIF (as part of a mixed drug ingestion) was associated with adverse drug reactions of nausea, vomiting, asthenia, dizziness, headache, abdominal pain and elevated amylase (< 1.5 times ULN). Both subjects recovered from these adverse events.

Treatment

There is no specific antidote for overdose with GIOTRIF. In cases of suspected overdose, GIOTRIF should be withheld and supportive care instituted.

PRESENTATION AND STORAGE CONDITIONS

GIOTRIF 20 mg – One tablet contains 20 mg afatinib (as afatinib dimaleate). The tablets are film-coated white to slightly yellowish, round, biconvex and bevel-edged. One side is debossed with the code “T20”, the other side is debossed with the Boehringer Ingelheim company symbol. GIOTRIF 20 mg are supplied in packs of 7*, 14* and 28 tablets.

GIOTRIF 30 mg – One tablet contains 30 mg afatinib (as afatinib dimaleate). The tablets are film-coated dark blue, round, biconvex and bevel-edged. One side is debossed with the code “T30”, the other side is debossed with the Boehringer Ingelheim company symbol. GIOTRIF 30 mg are supplied in packs of 7*, 14* and 28 tablets.

GIOTRIF 40 mg – One tablet contains 40 mg afatinib (as afatinib dimaleate). The tablets are film-coated light blue, round, biconvex and bevel-edged. One side is debossed with the code “T40”, the other side is debossed with the Boehringer Ingelheim company symbol. GIOTRIF 40 mg are supplied in packs of 7*, 14* and 28 tablets.

GIOTRIF 50 mg – One tablet contains 50 mg afatinib (as afatinib dimaleate). The tablets are film-coated dark blue, oval and biconvex. One side is debossed with the code “T50”, the other side is debossed with the Boehringer Ingelheim company symbol. GIOTRIF 50 mg are supplied in packs of 7*, 14* and 28 tablets.

Seven GIOTRIF film-coated tablets are packed in one perforated unit dose blister card consisting of a PVC/PVDC forming sheet and an aluminium lidding foil. One blister card is packed together with a desiccant sachet in a laminated aluminium pouch. One, two or

four pouches are packed into a carton box resulting in pack sizes of 7*, 14* or 28 film-coated tablets per pack, respectively.

*Not distributed in Australia.

Store below 30°C. Store in the original package in order to protect from moisture and light.

NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

07 November 2013

DATE OF MOST RECENT AMENDMENT

27 August 2015