Giotrif®

Boehringer Ingelheim

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 20 mg film-coated tablets
GIOTRIF 30 mg film-coated tablets
GIOTRIF 40 mg film-coated tablets
GIOTRIF 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 20 mg, 30 mg, 40 mg or 50 mg afatinib (as dimaleate).

Excipient with known effect:
GIOTRIF 20 mg: One film-coated tablet contains 118 mg lactose (as monohydrate).
GIOTRIF 30 mg: One film-coated tablet contains 176 mg lactose (as monohydrate).
GIOTRIF 40 mg: One film-coated tablet contains 235 mg lactose (as monohydrate).
GIOTRIF 50 mg: One film-coated tablet contains 294 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

GIOTRIF 20mg: white to slightly yellowish, round, biconvex, bevel-edged film-coated tablet debossed with the code T20 on one side and the Boehringer Ingelheim company symbol on the other side.

GIOTRIF 30mg: dark blue, round, biconvex, bevel-edged film-coated tabled debossed with the code T30 on one side and with the Boehringer Ingelheim company symbol on the other side.

GIOTRIF 40mg: light blue, round, biconvex, bevel-edged film-coated tablet debossed with the code T40 on one side and with the Boehringer Ingelheim company symbol on the other side.

GIOTRIF 50mg: dark blue, oval, biconvex, film-coated tablet debossed with the code T50 on one side and with the Boehringer Ingelheim company symbol on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- GIOTRIF is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s).
- GIOTRIF as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy

4.2 Dosage and Administration

The recommended dose of GIOTRIF is 40 mg orally once daily.

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 sections Interactions and Pharmacokinetics). 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 1 below).

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 1 (see section Adverse Reactions; for further details on management of specific drug related Adverse Events (AEs) see section Special Warnings and Precautions).

Table 1: 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, anti-diarrhoeal 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 section Special Warnings and 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.

Special populations

Patients with renal impairment

Exposure to afatinib was found to be increased in patients with moderate or severe renal impairment (see section Pharmacokinetics). Adjustments to the starting dose are not necessary in patients with mild, moderate or severe (eGFR 15-29 mL/min/1.73 m^2) renal impairment. Monitor patients with severe renal impairment and adjust GIOTRIF dose if not tolerated. GIOTRIF treatment in patients with eGFR <15 mL/min/1.73 m^2 or on dialysis 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 section 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 section Pharmacokinetics).

Paediatric population
The safety and efficacy of GIOTRIF have not been established in paediatric patients.
Treatment of children or adolescents with GIOTRIF was not supported by a clinical trial conducted in paediatric patients and is therefore not recommended.

Use of P-glycoprotein (P-gp) inhibitors
If P-gp inhibitors need to be taken, they should be administered using staggered dosing, ie. the P-gp inhibitor dose should be taken as far apart in time as possible from the GIOTRIF dose. This means preferably 6 hours (for P-gp inhibitors dosed twice daily) or 12 hours (for P-gp inhibitors dosed once daily) apart from GIOTRIF (see sections Special Warnings and Precautions, Interactions, and Pharmacokinetics).

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 min 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.

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

4.4 Special Warnings and 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 section Adverse Reactions). Diarrhoea may result in dehydration with or without renal impairment, which in rare cases has resulted in fatal outcomes. 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 anti-diarrhoeal agents especially within the first 6 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 section 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 section Adverse Reactions). 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 section 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 and toxic epidermal necrolysis. 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 section 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 patients treated with GIOTRIF across all clinical trials (including 0.5% of patients with CTCAE Grade ≥ 3 ILD-like adverse reactions) (see section Adverse Reactions). 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 section 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 comorbidities 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 section Dosage and administration). In patients who develop severe hepatic impairment while taking GIOTRIF, treatment should be discontinued.

Gastrointestinal perforations
Gastrointestinal perforation, including fatalities, has been reported during treatment with GIOTRIF in 0.2% of patients across all randomized controlled clinical trials. In the majority of cases, gastrointestinal perforation was associated with other known risk factors, including concomitant medications such as corticosteroids, NSAIDs, or anti-angiogenic agents, an underlying history of gastrointestinal ulceration, underlying diverticular disease, age, or bowel metastases at sites of perforation. In patients who develop gastrointestinal perforation while taking GIOTRIF, treatment should be permanently 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 section Adverse Reactions).

Left ventricular function

Left ventricular dysfunction has been associated with HER2 inhibition. Based on the available clinical trial data, there is no suggestion that GIOTRIF causes an adverse effect on cardiac contractility. However, 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 who 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.

P-glycoprotein (P-gp) interactions

Strong inhibitors of P-gp if administered prior to GIOTRIF may lead to increased exposure to afatinib. If P-gp inhibitors need to be taken, they should be administered using staggered dosing, preferably 6 hours or 12 hours apart from GIOTRIF. Concomitant treatment with strong inducers of P-gp may decrease exposure to afatinib (see sections Dosage and Administration, Interactions, and Pharmacokinetics).

4.5 Drug Interactions

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.

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. Therefore, it is recommended to administer strong P-gp inhibitors using staggered dosing, preferably 6 hours or 12 hours apart from GIOTRIF (see sections Dosage and Administration, Special Warnings and Precautions and Pharmacokinetics).

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

Interactions with 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).

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 sections Dosage and Administration and Pharmacokinetics).

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Non-clinical studies with afatinib have shown no signs of teratogenicity up to and including maternally lethal dose levels. Adverse changes were restricted to overtly toxic dose levels (see section Toxicology).

There are no studies in pregnant women using GIOTRIF. 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 foetus.

Breast-feeding

Based on non-clinical data (see section Toxicology), 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.

Fertility

Fertility studies in humans have not been performed with GIOTRIF. Available non-clinical toxicology data have shown effects on reproductive organs at higher doses (see section Toxicology). Therefore, an adverse effect of GIOTRIF therapy on human fertility cannot be excluded.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Adverse Reactions

Summary of the safety profile

The types of adverse reactions (ADRs) were generally associated with the EGFR inhibitory mode of action of afatinib. The summary of all ADRs is shown in Table 2. The most frequent ADRs were diarrhoea and skin related adverse events (see section Special Warnings and Precautions) as well as stomatitis and paronychia (see also Table 3, 4 and 5). Overall, dose reduction (see section Dosage and Administration) led to a lower frequency of common adverse reactions.

In patients treated with once daily GIOTRIF 40 mg, dose reductions due to ADRs occurred in 57% of the patients in LUX-Lung 3 trial and in 25% of the patients in the LUX-Lung 8 trial. Discontinuation due to ADRs diarrhoea and rash/acne was 1.3% and 0% in LUX-Lung 3 and 3.8% and 2.0% in LUX-Lung 8, respectively. ILD-like adverse reactions were reported in 0.7% of afatinib treated patients. Bullous, blistering and exfoliative skin conditions have been reported including rare cases suggestive of Stevens-Johnson syndrome and toxic epidermal necrolysis although in these cases there were potential alternative aetiologies (see section Special Warnings and Precautions").

In the pivotal LUX-Lung 8 (1200.125) trial a total of 392 patients with Squamous NSCLC were treated with GIOTRIF with a starting dose of 40 mg once daily and a total of 395 patients were treated with 150 mg erlotinib once daily. After the first treatment cycle (28 days) the dose of GIOTRIF was escalated to 50 mg in 39 (10%) patients. The overall incidence of ADRs in patients treated with GIOTRIF or erlotinib was 93% vs. 81% respectively. The incidence of diarrhoea ADRs was higher in the GIOTRIF-treated patients compared to erlotinib (70% vs. 33%), while incidence of rash/acne was similar in both groups (67% vs. 67%). Dose reductions due to adverse events occurred in 27% of GIOTRIF-treated patients. Treatment was discontinued due to ADRs in 11% of patients treated with GIOTRIF, and in 5% of erlotinib treated patients.

Tabulated list of adverse reactions

Table 2 summarises the frequencies of ADRs pooled from all NSCLC trials and from post-marketing experience with daily GIOTRIF doses of 40 mg (N=497) or 50 mg (N=1638) as monotherapy. The following terms are used to rank the ADRs by frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each

frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Summary of ADRs per frequency category

Body System	Very common	Common	Uncommon	Rare
Infections and infestations	Paronychia[1]	Cystitis		
Metabolism and nutrition disorders	Decreased appetite	Dehydration Hypokalaemia		
Nervous system disorders		Dysgeusia		
Eye disorders		Conjunctivitis Dry eye	Keratitis	
Respiratory, thoracic and mediastinal disorders	Epistaxis	Rhinorrhoea	Interstitial lung disease	
Gastrointestinal disorders	Diarrhoea Stomatitis[2] Nausea Vomiting	Dyspepsia Cheilitis	Pancreatitis Gastrointestinal perforation	
Hepatobiliary disorders		Alanine aminotransferase increased Aspartate aminotransferase increased		
Skin and subcutaneous tissue disorders	Rash[3] Dermatitis acneiform[4] Pruritus[5] Dry skin[6]	Palmar-plantar erythrodysaesthesia syndrome Nail Disorders[8]		Stevens-Johnson syndrome[7] Toxic epidermal necrolysis[7]
Musculoskeletal and connective tissue disorders		Muscle spasms		
Renal and urinary disorders		Renal impairment/ Renal failure		
General disorders and administration site conditions		Pyrexia		
Investigations		Weight decreased		

[1] Includes Paronychia, Nail infection, Nail bed infection

[2] Includes Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Oral mucosa erosion, Mucosal erosion, Mucosal ulceration

[3] Includes group of rash preferred terms
[4] Includes Acne, Acne pustular, Dermatitis acneiform
[5] Includes Pruritus, Pruritus generalised
[6] Includes Dry skin, Skin chapped
[7] Based on post-marketing experience
[8] Includes Nail disorder, Onycholysis, Nail toxicity, Onychoclasis, Ingrowing nail, Nail pitting, Onychomadesis, Nail discoloration, Nail dystrophy, Nail ridging, and Onychogryphosis

Description of selected adverse reactions

Very common ADRs in GIOTRIF-treated patients occurring in at least 10% of patients in trial LUX-Lung 3 and LUX- Lung 7 are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Tables 3 and 4.

Table 3: Very common ADRs in trial LUX-Lung 3

	GIOTRIF (40 mg/day) N=229			**Pemetrexed/ Cisplatin** N=111		
NCI-CTC Grade	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Infections and infestations						
Paronychia[1]	57.6	11.4	0	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	20.5	3.1	0	53.2	2.7	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	13.1	0	0	0.9	0.9	0
Gastrointestinal disorders						
Diarrhoea	95.2	14.4	0	15.3	0	0
Stomatitis[2]	69.9	8.3	0.4	13.5	0.9	0
Cheilitis	12.2	0	0	0.9	0	0
Skin and subcutaneous tissue disorders						
Rash[3]	70.3	14	0	6.3	0	0
Dermatitis acneiform[4]	34.9	2.6	0	0	0	0
Dry skin[5]	29.7	0.4	0	1.8	0	0
Pruritus[6]	19.2	0.4	0	0.9	0	0
Investigations						
Weight decreased	10.5	0	0	9.0	0	0

[1] Includes Paronychia, Nail infection, Nail bed infection
[2] Includes Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Oral mucosa erosion, Mucosal erosion, Mucosal ulceration
[3] Includes group of rash preferred terms
[4] Includes Acne, Acne pustular, Dermatitis acneiform
[5] Includes Dry skin, Skin chapped
[6] Includes Pruritus, Pruritus generalised

The safety of GIOTRIF monotherapy in patients with squamous cell carcinoma of the lung receiving 40 mg starting dose was assessed in trial LUX-Lung 8. The most frequent ADRs were associated with the EGFR inhibitory mode of action of GIOTRIF and were consistent with trials LUX-Lung 3 and LUX-Lung 1 in patients with adenocarcinoma of the lung. The majority of patients with ADRs (65%) had Grade 1 or 2 events. The

ADR of CTCAE grade 3 / 4 diarrhoea occurred in 9.9% / 0.5% of patients. The rate of drug-related CTCAE grade 3 rash was 5.9%. ADRs led to discontinuation of treatment for 11% of patients. Discontinuation of treatment due to ADRs diarrhoea and rash/acne regardless of severity grade occurred in 3.8% and 2.0% of patients.

Table 4: Very common ADRs in trial LUX-Lung 7

	GIOTRIF (40 mg/day) N=160			**Gefitinib** N=159		
NCI-CTC Grade	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Infections and infestations						
Paronychia[1]	57.5	1.9	0	17.0	0.6	0
Cystitis[2]	11.3	1.3	0	7.5	1.3	0.6
Metabolism and nutrition disorders						
Decreased appetite	27.5	1.3	0	24.5	1.9	0
Hypokalaemia[3]	10.6	2.5	1.3	5.7	1.3	0
Respiratory, thoracic and mediastinal disorders						
Rhinorrhoea[4]	19.4	0	0	7.5	0	0
Epistaxis	18.1	0	0	8.8	0	0
Gastrointestinal disorders						
Diarrhoea	90.6	13.8	0.6	64.2	3.1	0
Stomatitis[5]	64.4	4.4	0	27.0	0	0
Nausea	25.6	1.3	0	27.7	1.3	0
Vomiting	19.4	0.6	0	13.8	2.5	0
Dyspepsia	10.0	0	0	8.2	0	0
Hepatobiliary disorders						
Alanine aminotransferase increased	11.3	0	0	27.7	8.8	0.6
Skin and subcutaneous tissue disorders						
Rash[6]	80.0	7.5	0	67.9	3.1	0
Dry skin	32.5	0	0	39.6	0	0
Pruritus[7]	25.6	0	0	25.2	0	0
Dermatitis acneiform[8]	23.8	1.9	0	32.1	0.6	0
General disorders and administration site conditions						
Pyrexia	13.8	0	0	6.3	0	0
Investigations						
Weight decreased	10.0	0.6	0	5.7	0.6	0

[1] Includes Paronychia, Nail infection, Nail bed infection
[2] Includes Cystitis, Urinary tract infection
[3] Includes Hypokalaemia, Blood potassium decreased
[4] Includes Rhinorrhoea, Nasal inflammation
[5] Includes Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Mucosal erosion
[6] Includes group of rash preferred terms
[7] Includes Pruritus, Pruritus generalised
[8] Includes Dermatitis acneiform, Acne

Liver function test abnormalities

Liver function test abnormalities (including elevated ALT and AST) were observed in patients receiving

GIOTRIF 40 mg. These elevations were mainly transient and did not lead to discontinuation. Grade 2 (> 2.5 to 5.0 times upper limit of normal (ULN)) ALT elevations occurred in < 8% of patients treated with this medicinal product. Grade 3 (> 5.0 to 20.0 times ULN) elevations occurred in <4% of patients treated with GIOTRIF (see "Special warnings and precautions").

Description of selected adverse reactions

Very common ADRs in GIOTRIF-treated patients occurring in at least 10% of patients in trial LUX-Lung 8 are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 5.

Table 5: Very common ADRs in trial LUX-Lung 8*

	GIOTRIF (40 mg/day) N=392			**Erlotinib** N=395		
NCI-CTC Grade	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Infections and infestations						
Paronychia[1]	11.0	0.5	0	5.1	0.3	0
Metabolism and nutrition disorders						
Decreased appetite	24.7	3.1	0	26.1	2.0	0
Gastrointestinal disorders						
Diarrhoea	74.7	9.9	0.8	41.3	3.0	0.3
Stomatitis[2]	30.1	4.1	0	10.6	0.5	0
Nausea	20.7	1.5	0	16.2	1.0	0.3
Skin and subcutaneous tissue disorders						
Rash[3]	60.7	5.4	0	56.7	8.1	0
Dermatitis acneiform[4]	14.0	1.3	0	18.0	2.5	0

* Reporting the frequency of patients with all causality AEs

[1] Includes Paronychia, Nail infection, Nail bed infection

[2] Includes Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Oral mucosa erosion, Mucosal erosion, Mucosal ulceration

[3] Includes group of rash preferred terms

[4] Includes Acne, Acne pustular, Dermatitis acneiform

Liver function test abnormalities

Liver function test abnormalities (including elevated ALT and AST) were observed in patients receiving GIOTRIF 40 mg. These elevations were mainly transient and did not lead to discontinuation. Grade 2 ALT elevations occurred in 1% and Grade 3 elevations occurred in 0.8% of patients treated with GIOTRIF (see section Special Warnings and Precautions).

4.9 Overdose

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.
If indicated, elimination of unabsorbed afatinib may be achieved by emesis or gastric lavage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antineoplastic agents – protein kinase inhibitors, ATC code:L01EB03.

Mechanism of action
Afatinib is a potent and selective, irreversible ErbB Family Blocker. Afatinib covalently binds to and irreversibly blocks signalling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER2 (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 or receptor overexpression contributes to the malignant phenotype in subsets of patients across multiple cancer types.
In non-clinical disease models with ErbB pathway deregulation, afatinib as a single agent effectively blocks ErbB receptor signalling resulting in tumour growth inhibition or tumour regression. NSCLC models with either L858R or Del 19 EGFR mutations are particularly sensitive to afatinib treatment.
The acquisition of a secondary T790 mutation is a major mechanism of acquired resistance to afatinib and gene dosage of the T790M – containing allele correlates with the degree of resistance in vitro. The T790M mutation is found in approximately 50% of patients' tumours upon disease progression on afatinib, for which T790M targeted EGFR TKIs may be considered as a next line treatment option.

Clinical trials

GIOTRIF in Non-Small Cell Lung Cancer (NSCLC)

The efficacy and safety of GIOTRIF® as second line treatment of patients with NSCLC of squamous histology was investigated in an open-label active controlled trial LUX-Lung 8.

GIOTRIF *in EGFR mutation positive patients naïve to EGFR TKI treatment*

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, multicenter, 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 the first treatment cycle (21 days) if patients

had no or limited drug-related adverse events (i.e. absence of diarrhoea, skin rash, stomatitis, and/or other drug related events above CTCAE Grade 1), were compliant, and had no prior dose reduction.

Among the patients randomized, 65% were female, the median age was 61 years, the baseline ECOG performance status was 0 (39%) or 1 (61%), 72% were Asian and 26% were Caucasian. The majority of patients had a tumour sample with an EGFR mutation categorized as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while the remaining 11% had other mutations.

The primary endpoint of PFS (independent review, 221 events) showed a statistically significant improvement in PFS for patients treated with GIOTRIF compared with patients treated with chemotherapy (median PFS 11.1 vs. 6.9 months). When comparing the pre-specified subgroup of common (L858R or Del 19) EGFR mutations, the difference in PFS was further pronounced (median PFS: 13.6 vs 6.9 months). The percentages of patients being alive and progression-free (PFS rate) at 12 months were 46.5% in patients treated with GIOTRIF and 22% in patients treated with chemotherapy for the overall trial population, and 51.1% vs. 21.4% in the subgroup of common mutations.

The Kaplan-Meier curves of the primary PFS analysis are shown in Figure 1, and efficacy results are summarised in Table 6. At the time of primary PFS analysis, a total of 45 (20%) patients treated with GIOTRIF and 3 (3%) patients treated with chemotherapy were known to be alive and progression-free and thus censored in Figure 1.

Figure 1: Kaplan-Meier Curves for PFS by independent review by treatment group in LUX-Lung 3 Trial (Overall Population):

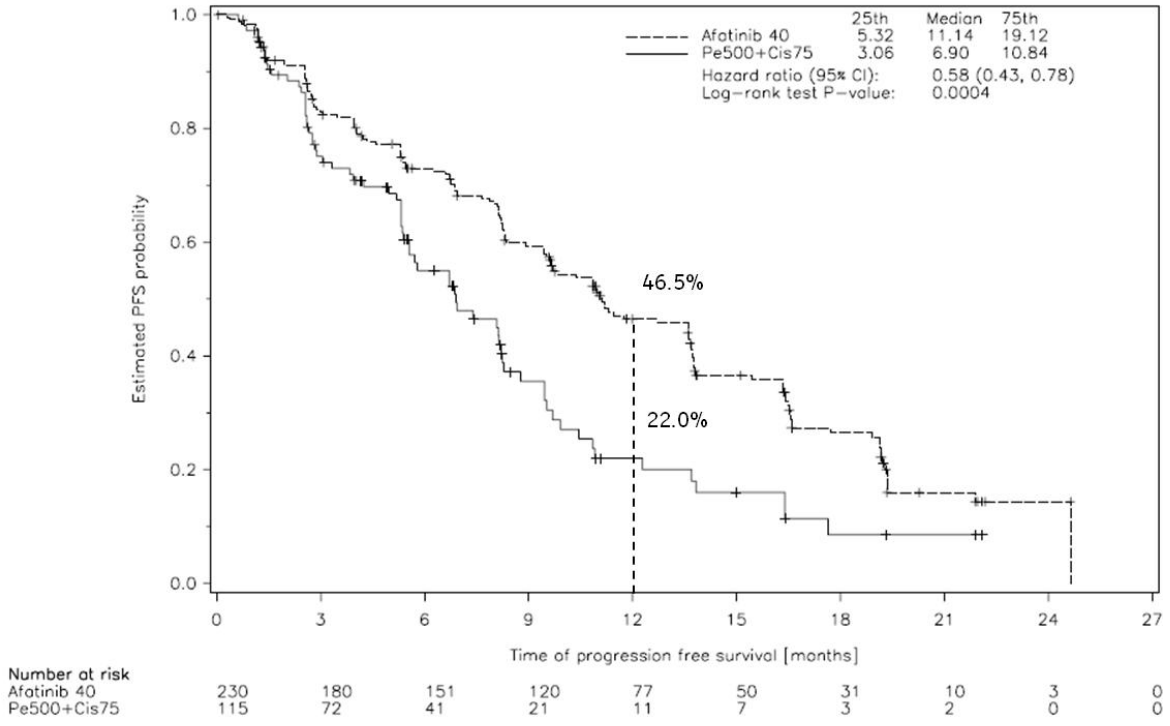


Table 6: Efficacy results of GIOTRIF vs. pemetrexed/cisplatin (LUX-Lung 3 Trial) based on the primary PFS analysis as of 9 February 2012 (Independent review)

	GIOTRIF (N=230)	**Pemetrexed/ Cisplatin** (N=115)	**Hazard Ratio/ Odds Ratio (95%CI) p-value[4]**
PFS, Overall Trial Population **Months (median)** **1-year PFS Rate** **18-months PFS Rate**	 **11.1** 46.5% 26.4%	 **6.9** 22% 8.6%	 HR 0.58 (0.43-0.78) 0.0004
PFS, Patients with L858R or Del 19 Mutations [1] **Months (median)** **1-year PFS Rate** **18-months PFS Rate**	 **13.6** 51.1% 28.6%	 **6.9** 21.4% 7.4%	 HR 0.47 (0.34-0.65) < 0.0001
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

[4] p-value for PFS/OS based on stratified log-rank test; p-value for Objective Response Rate and Disease Control Rate based on logistic regression

In the pre-defined EGFR mutation subgroups, the median OS with first-line GIOTRIF vs chemotherapy was 33.3 months vs 21.1 months (HR=0.54, (95% CI 0.36-0.79), p=0.0015) in patients with Del19 (n=169) and 27.6 months vs 40.3 months (HR=1.30, (95% CI: 0.80-2.11), p=0.2919) in patients with L858R (n=138).

PFS benefit was accompanied by improvement in disease-related symptoms and delayed time to deterioration (see Table 7). Mean scores over time for overall quality of life, global health status and physical, role, and cognitive functioning were significantly better for GIOTRIF.

Table 7: Symptom outcomes for GIOTRIF vs. chemotherapy in LUX-Lung 3 trial (EORTC QLQ-C30 & QLQ-LC13)

	LUX-Lung 3		
	Cough	**Dyspnoea**	**Pain**
% of patients improved [a]	67% vs. 60%; p=0.2133	65% vs. 50%; p=0.0078	60% vs. 48%; p=0.0427
Delay of median time to deterioration (months) [a,b]	27.0 vs. 8.0 HR 0.60; p=0.0062	10.4 vs. 2.9 HR 0.68; p=0.0129	4.2 vs. 3.1 HR 0.83; p=0.1882

[a] values presented for GIOTRIF vs. chemotherapy, p-value based on logistic regression
[b] p-value for time to deterioration based on stratified log-rank test

LUX-Lung 7 (1200.123)

LUX-Lung 7 is a randomised, global, open label Phase IIb trial investigating the efficacy and safety of GIOTRIF in patients with locally advanced or metastatic lung adenocarcinoma (stage IIIB or IV) with EGFR mutations in the first-line setting. Patients were screened for the presence of activating EGFR mutations (Del 19 and/or L858R) using the TheraScreen® EGFR RGQ PCR Kit, Qiagen Manchester Ltd. Patients (N=319) were randomised (1:1) to receive GIOTRIF® 40 mg orally once daily (N=160) or gefitinib 250 mg orally once daily (N=159). Randomisation was stratified according to EGFR mutation status (Del 19; L858R) and presence of brain metastases (yes; no).

Among the patients randomised, 62% were female, the median age was 63 years, 16% of patients had brain metastases, the baseline ECOG performance status was 0 (31%) or 1 (69%), 57% were Asian and 43% were non-Asian. Patients had a tumour sample with an EGFR mutation categorized as either exon 19 deletion (58%) or exon 21 L858R substitutions (42%).

The co-primary endpoints include PFS by independent review and OS. Secondary endpoints include ORR and DCR. GIOTRIF significantly improved PFS and ORR in EGFR mutation positive patients compared to gefitinib. The efficacy results are summarized in Table 8.

Table 8: Efficacy results of GIOTRIF vs. gefitinib (LUX-Lung 7) based on primary analysis as of August 2015.

	GIOTRIF (N=160)	**Gefitinib** (N=159)	**Hazard Ratio/ Odds Ratio (95%CI) p-value[2]**
Median PFS (months), Overall Trial Population	11.0	10.9	HR 0.73 (0.57-0.95) 0.0165
18-months PFS rate	27%	15%	
24-months PFS rate	18%	8%	
Median OS (months)[1], Overall Trial Population	27.9	24.5	HR 0.86 (0.66, 1.12) 0.2580
Alive at 18-months	71%	67%	
Alive at 24-months	61%	51%	
Objective Response Rate (CR+PR)[3]	70%	56%	OR 1.87 (1.12, 2.99) 0.0083

[1]OS results based on primary OS analysis as of April 2016 at event rates of 109 (68.1%) and 117 (73.6%) in the GIOTRIF and gefitinib arms, respectively

[2]p-value for PFS/OS based on stratified log-rank test; p-value for Objective Response Rate based on stratified logistic regression

[3]CR=complete response; PR=partial response

The PFS hazard ratio for patients with DEL 19 mutations and L858R mutations was 0.76 (95% CI [0.55, 1.06]; p=0.1071), and 0.71 (95% CI [0.47, 1.06]; p=0.0856) respectively for afatinib vs gefitinib.

Analysis of GIOTRIF's efficacy in EGFR TKI naïve patients with tumours harbouring uncommon EGFR Mutations (LUX-Lung 2, -3, and -6)

In three clinical trials of GIOTRIF with prospective tumour genotyping (Phase 3 trials LUX-Lung 3 and – 6, and single arm Phase 2 trial LUX-Lung 2), an analysis was conducted of data from a total of 75 TKI-naive patients with advanced (stage IIIb–IV) lung adenocarcinomas harbouring uncommon EGFR mutations, which were defined as all mutations other than Del 19 and L858R mutations. Patients were treated with GIOTRIF 40 mg (all three trials) or 50 mg (LUX-Lung 2) orally once daily.

In patients with tumours harbouring either G719X (N=18), L861Q (N=16), or S768I substitution mutation (N=8), the confirmed ORR was 72.2%, 56.3%, 75.0%, respectively, and the median duration of response was 13.2 months, 12.9 months and 26.3 months, respectively (see table 9).

Table 9: Efficacy of GIOTRIF in patients whose tumours have specific uncommon and common EGFR mutations

	Uncommon EGFR mutations			**Common EGFR mutations**	
	G719X N = 18	**L861Q N = 16**	**S768I N = 8**	**L858R N = 237[a]**	**Del19 N = 288[b]**
Patients with OR[c], N (%)	13 (72.2)	9 (56.3)	6 (75.0)	124 (52.3)	195 (67.7)
Median duration of OR[c] (95% CI), months	13.24 (6.77, NE)	12.91 (2.79, 20.63)	26.27 (4.11, 37.29)	12.39 (9.23, 14.29)	12.45 (10.15, 14.85)

Patients with DC[d], N (%)	16 (88.9)	14 (87.5)	8 (100.0)	213 (89.9)	269 (93.4)
Median PFS (95% CI), months	13.80 (6.77, NE)	8.18 (4.53, 16.59)	15.66 (2.56, 41.26)	9.86 (8.31, 13.67)	13.70 (11.14, 13.90)
Median OS (95% CI), months	26.94 (16.43, NE)	17.12 (15.34, 21.55)	NE (3.42, NE)	23.10 (19.65, 26.81)	32.95 (29.31, 37.45)

Abbreviations: DC = disease control, NE = Not estimable, OR = objective response
[a] All afatinib-treated patients from trials 1200.22, 1200.32, and 1200.34 whose tumours have the common EGFR mutation L858R only
[b] All afatinib-treated patients from trials 1200.22, 1200.32, and 1200.34 whose tumours have the common EGFR mutation Del19 only
[c] Confirmed objective response
[d] Confirmed disease control

In patients with tumours harbouring exon 20 insertions (N=23) the confirmed ORR was 8.7% and the median duration of response was 7.1 months. In patients with tumours harbouring de-novo T790M mutations (N=14) the confirmed ORR was 14.3% and the median duration of response was 8.3 months.

GIOTRIF in patients with NSCLC of squamous histology

LUX-Lung 8 (1200.125)

The efficacy and safety of GIOTRIF as second-line treatment for patients with advanced NSCLC of squamous histology was investigated in a randomized open-label global Phase III trial LUX-Lung 8. Patients who received at least 4 cycles of platinum-based therapy in the first line setting were subsequently randomized 1:1 to daily GIOTRIF 40 mg or erlotinib 150 mg until progression. Dose escalation of GIOTRIF to 50 mg was allowed after first cycle (28 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 CTCAE Grade 1), compliant dosing and no prior dose reduction. Randomization was stratified by race (Eastern Asian vs non Eastern Asian). The primary endpoint was PFS (analysed when at least 372 events were reported by independent review); OS was the key secondary endpoint (analysed at first 632 deaths). Other secondary endpoints included ORR, DCR, change in tumour size and HRQOL.
Among 795 patients randomized, the majority were males (83.8%), white (72.8%), current or former smokers (91.6%) with baseline performance status ECOG 1 (66.8%).
Second-line GIOTRIF significantly improved PFS and OS of patients with squamous NSCLC compared to erlotinib. In the primary PFS analysis median PFS was 2.43 months in the GIOTRIF group and 1.94 month on erlotinib (HR=0.82, 95% CI (0.676, 0.998), p=0.0427). The final PFS analysis including all randomized patients confirmed earlier results (Table 10). The primary analysis of OS demonstrated significant reduction in the risk of death for patients treated with GIOTRIF compared with erlotinib (HR=0.81 95% CI (0.69, 0.95), p=0.0077) with significantly higher proportions of GIOTRIF-treated patients alive at the landmark points throughout the period of observation such as 12 and 18 months post randomization.
The rates of objective tumour response and stabilization of disease were higher with GIOTRIF. The median duration of response was 7.29 months on GIOTRIF and 3.71 on erlotinib.

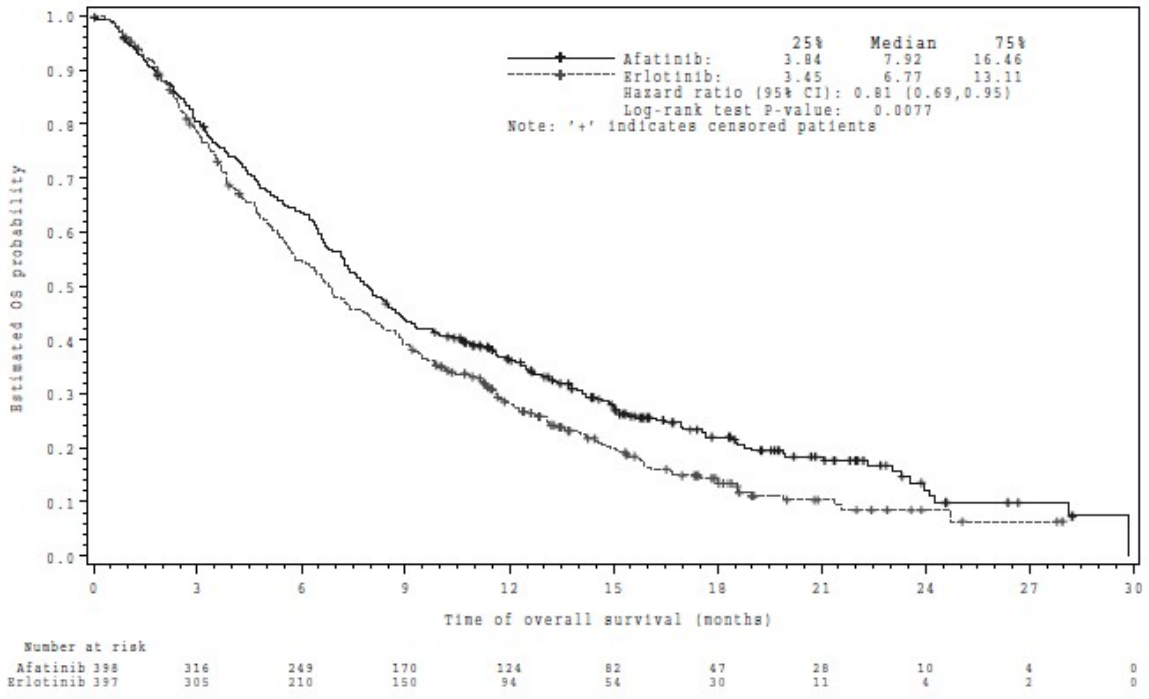
Table 10: Efficacy results for GIOTRIF vs erlotinib in LUX-Lung 8, based on primary analysis of OS, including all randomized patients

	GIOTRIF (N=398)	**Erlotinib** **(n=397)**	**Hazard Ratio/ Odds Ratio (95%CI) p-value[a]**
PFS **Months (median)**	2.63	1.94	HR 0.81 (0.69, 0.96) 0.0103
OS **Months (median)** **Alive at 12 months** **Alive at 18 months**	7.92 36.4% 22.0%	6.77 28.2% 14.4%	HR 0.81 (0.69, 0.95) 0.0077
Objective Response Rate (CR+PR) [b]	**5.5%**	**2.8%**	OR 2.06 (0.98, 4.32) 0.0551
Disease Control Rate (CR+PR+SD) [b]	**50.5%**	**39.5%**	OR 1.56 (1.18, 2.06) 0.0020

[a]p-value for PFS/OS based on stratified log-rank test; p-value for Objective Response Rate and Disease Control Rate based on logistic regression

[b] CR=complete response; PR=partial response; SD=stable disease

Figure 2 Kaplan-Meier Curves for OS by treatment group in LUX-Lung 8



PFS benefit was accompanied by improvement in disease-related symptoms and delayed time to deterioration (see Table 11).

Table 11: Symptom outcomes for GIOTRIF vs. erlotinib in trial LUX-Lung 8 (EORTC QLQ-C30 & QLQ-LC13)

	Cough	**Dyspnoea**	**Pain**
% of patients improved [a,c]	43% vs. 35%; p=0.0294	51% vs. 44%; p=0.0605	40% vs. 39%; p=0.7752
Delay of time to deterioration (months)[b,c]	4.5 vs. 3.7 HR 0.89; p=0.2562	2.6 vs. 1.9 HR 0.79; p=0.0078	2.5 vs. 2.4 HR 0.99; p=0.8690

[a] values presented for GIOTRIF vs. erlotinib, p-value based on logistic regression
[b] p-value for time to deterioration based on stratified log-rank test
[c] p-values were not adjusted for multiplicity

5.2 Pharmacokinetics properties

Absorption and distribution

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 sections Dosage and administration and Interactions). After administration of GIOTRIF, the mean relative bioavailability was 92% (adjusted gMean ratio of $AUC_{0-\infty}$) when compared to an oral solution.
In vitro binding of afatinib to human plasma proteins is approximately 95%.

Metabolism and excretion

Enzyme-catalyzed metabolic reactions play a negligible role for afatinib *in vivo*. Covalent adducts to proteins are the major circulating metabolites of afatinib.
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. Exposure to afatinib in subjects with renal impairment was compared to healthy volunteers following a single dose of 40 mg GIOTRIF. Subjects with moderate renal impairment (n=8; eGFR 30-59 mL/min/1.73m², according to the Modification of Diet in Renal Disease [MDRD] formula) had an exposure of 101% (C_{max}) and 122% (AUC_{0-tz}) in comparison to their healthy controls. Subjects with severe renal impairment (n=8; eGFR 15-29 mL/min/1.73m², according to the MDRD formula) had an exposure of 122% (C_{max}) and 150% (AUC_{0-tz}) in comparison to their healthy controls. Based on this trial and population pharmacokinetic analysis of data derived from clinical trials in various tumour types, it is concluded, that adjustments to the starting dose in patients with mild (eGFR 60-89 mL/min/1.73m²), moderate (eGFR 30-59 mL/min/1.73m²), or severe (eGFR 15-29 mL/min/1.73m²) renal impairment are not necessary, but patients with severe impairment should be monitored (see sections Population

pharmacokinetic analysis in special populations below and section Dosage and Administration). GIOTRIF has not been studied in patients with eGFR <15 mL/min/1.73m² or on dialysis.

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 section Population pharmacokinetic analysis in special populations below). No starting dose adjustments appear necessary in patients with mild or moderate hepatic impairment (see section Dosage and Administration). The pharmacokinetics of afatinib had not been studied in subjects with severe (Child Pugh C) hepatic dysfunction (see section Special Warnings and 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 to 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.

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 phospatase 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 section Dosage and Administration, Special Warnings and Precautions, and Interactions).

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 section Special Warnings and Precautions and Interactions).

Effect of afatinib on P-gp Substrates
Based on *in vitro* data, afatinib is a moderate inhibitor of P-gp. 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 OATP1B1, 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-catalyzed metabolic reactions play a negligible role for the metabolism of afatinib. Approximately 2% of the afatinib dose was metabolized by FMO3 and the CYP3A4-dependent N-demethylation was too low to be quantitatively detected.

Effect of afatinib on CYP enzymes
Afatinib is not 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.

Pharmacodynamics

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. This suggests that GIOTRIF does not have a relevant effect on the QTcF interval.

5.3 Toxicology

Oral administration of single doses to mice and rats indicated a low acute toxic potential of afatinib. In oral repeated-dose studies for up to 26 weeks in rats or 52 weeks in minipigs the main effects were identified in the skin (dermal changes, epithelial atrophy and folliculitis in rats), the gastrointestinal tract (diarrhoea, erosions in the stomach, epithelial atrophy in rats and minipigs) and the kidneys (papillary necrosis in rats). Depending on the finding, these changes occurred at exposures below, in the range of or above clinically relevant levels. Additionally, in various organs pharmacodynamically mediated atrophy of epithelia was observed in both species.

Reproduction toxicity
Based on the mechanism of action, GIOTRIF has the potential to cause foetal harm. The embryo-foetal development studies performed on afatinib revealed no indication of teratogenicity up to dose levels including maternal death. Changes identified were restricted to skeletal alterations consisting of incomplete ossifications/unossified elements (rat) and abortions at maternally toxic dose, reduced foetal weights as well as mainly visceral and dermal variations (rabbit). The respective total systemic exposure (AUC) was either slightly above (2.2 times in rats) or below (0.3 times in rabbits) compared with levels in patients.

Radiolabelled afatinib administered orally to rats on Day 11 of lactation was excreted into milk of the dams. 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.

A fertility study in male and female rats by the oral route up to the maximum tolerated dose revealed no significant impact on fertility. The total systemic exposure (AUC_{0-24}) that could be achieved in male and female rats was in the range or less than that observed in patients (1.3 times and 0.51 times, respectively). A study in rats by the oral route up to the maximum tolerated doses revealed no significant impact on pre-/postnatal development. Effects were limited to lower birth weight and body weight gain of offspring but without materially affecting the attainment of developmental landmarks, sexual maturation or performance with behavioural assessments. The highest total systemic exposure (AUC_{0-24}) that could be achieved in female rats was less than that observed in patients (0.23 times).

Phototoxicity
An *in vitro* 3T3 phototoxicity test with afatinib was performed. It was concluded that GIOTRIF may have phototoxicity potential.

Carcinogenicity
Carcinogenicity studies have not been conducted with afatinib.
A marginal response to afatinib was observed in a single tester strain of a bacterial (Ames) mutagenicity assay. However, no mutagenic or genotoxic potential could be identified in an *in vitro* chromosomal aberration test at non-cytotoxic concentrations as well as the *in vivo* bone marrow micronucleus assay, the *in vivo* Comet assay and an *in vivo* 4-week oral mutation study in the Muta™ Mouse.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet Core: Lactose monohydrate, microcrystalline cellulose (E460), colloidal anhydrous silica (E551), crospovidone, magnesium stearate (E470b).

Film-coating: Hypromellose 2910 (E464), macrogol 400, titanium dioxide (E171), talc (E553b), polysorbate 80 (E433), Colourant containing indigo carmine (E132) aluminium hydroxide (only used for 50 mg, 40 mg and 30 mg tablets)

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.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to the packaging for information on shelf-life.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container Seven x 1 film-coated tablet per PVC/PVDC/Aluminium blister. Each blister is packed together with a dessicant sachet in a laminated aluminium pouch. Cartons containing 4 blister strips (4 x 7 film-coated tablets).

7. PRODUCT OWNER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

Date of revision: 4 February 2022

Store in a safe place out of the reach of children!