GIOTRIF®
Afatinib (as dimaleate)
Film coated tablets

PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 20 mg
GIOTRIF 30 mg
GIOTRIF 40 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GIOTRIF 20 mg, film coated tablets
One film-coated tablet contains 20 mg afatinib (as dimaleate).
Excipient with known effect
One film-coated tablet contains 124 mg lactose (as monohydrate).

GIOTRIF 30 mg, film coated tablets
One film-coated tablet contains 30 mg afatinib (as dimaleate).
Excipient with known effect
One film-coated tablet contains 186 mg lactose (as monohydrate).

GIOTRIF 40 mg, film coated tablets
One film-coated tablet contains 40 mg afatinib (as dimaleate).
Excipient with known effect
One film-coated tablet contains 248 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

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

GIOTRIF 30 mg
Dark blue, round, biconvex and bevel-edged film-coated tablet debossed with the code "T30" on one side and the Boehringer Ingelheim company logo on the other.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GIOTRIF as monotherapy is indicated for the treatment of:

- Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s);

- locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy (see section 5.1).

4.2 Posology and method of administration

Treatment with GIOTRIF should be initiated and supervised by a physician experienced in the use of anticancer therapies.

EGFR mutation status should be established prior to initiation of GIOTRIF therapy (see section 4.4).

Posology
The recommended dose is 40 mg once daily.

This medicinal product should be taken without food. Food should not be consumed for at least 3 hours before and at least 1 hour after taking this medicinal product (see sections 4.5 and 5.2).

GIOTRIF treatment should be continued until disease progression or until no longer tolerated by the patient (see Table 1 below).

Dose escalation
A dose escalation to a maximum of 50 mg/day may be considered in patients who tolerate a 40 mg/day starting dose (i.e. absence of diarrhoea, skin rash, stomatitis, and other adverse reactions with CTCAE Grade > 1) in the first cycle of treatment (21 days for EGFR mutation positive NSCLC and 28 days for squamous NSCLC). The dose should not be escalated in any patients with a prior dose reduction. The maximum daily dose is 50 mg.

Dose adjustment for adverse reactions
Symptomatic adverse reactions (e.g. severe/persistent diarrhoea or skin related adverse reactions) may be successfully managed by treatment interruption and dose reductions or treatment discontinuation of GIOTRIF as outlined in Table 1 (see sections 4.4 and 4.8).

Table 1: Dose adjustment information for adverse reactions

CTCAE[a] Adverse reactions	**Recommended dosing**	
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
[b] In case of diarrhoea, anti-diarrhoeal medicinal products (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 treatment should be interrupted pending evaluation. If ILD is diagnosed, GIOTRIF should be discontinued and appropriate treatment initiated as necessary (see section 4.4).

Missed dose
If a dose is missed, it should be taken within 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.

Use of P-glycoprotein (P-gp) inhibitors
If P-gp inhibitors need to be taken, they should be administered using staggered dosing, i.e. 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 section 4.5).

Special populations

Patients with renal impairment
Exposure to afatinib was found to be increased in patients with moderate or severe renal impairment (see section 5.2). Adjustments to the starting dose are not necessary 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. Monitor patients with severe renal impairment (eGFR 15-29 mL/min/1.73m²) and adjust GIOTRIF dose if not tolerated.
GIOTRIF treatment in patients with eGFR <15 mL/min/1.73m² 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 5.2). Adjustments to the starting dose are not necessary in patients with mild or moderate hepatic impairment. This medicinal product has not been studied in patients with severe (Child Pugh C) hepatic impairment. Treatment in this population is not recommended (see section 4.4).

Paediatric population
There is no relevant use of GIOTRIF in the paediatric population in the indication of NSCLC.
Treatment of children or adolescents with GIOTRIF was not supported by a clinical trial conducted in paediatric patients with other conditions (see sections 5.1 and 5.2). Safety and efficacy have not been established.
Therefore, treatment of children or adolescents with this medicinal product is not recommended.

Method of administration
This medicinal product is for oral use. The tablets should be swallowed whole with water. If swallowing of whole tablets is not possible, these can be dispersed in approximately 100 mL of non-carbonated 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 it 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

Hypersensitivity to afatinib or to any of the excipients listed in section 6.1.
If you are pregnant or breastfeeding.

4.4 Special warnings and precautions for use

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 4.8). 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 medicinal products especially within the first 6 weeks of the treatment is important and should start at first signs of diarrhoea. Antidiarrhoeal medicinal products (e.g. loperamide) should be used and if necessary their dose

should be escalated to the highest recommended approved dose. Anti-diarrhoeal medicinal products 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 4.2). 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 this medicinal product (see section 4.8). 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 use of sun screen is advisable. Early intervention (such as emollients, antibiotics) of dermatologic reactions can facilitate continuous GIOTRIF treatment. Patients with severe skin reactions may also require temporary interruption of therapy, dose reduction (see section 4.2), 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. Treatment with this medicinal product should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions (see section 4.8).

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 5.2). This could result in a higher risk of developing adverse reactions in particular 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 adverse reactions (such as lung infiltration, pneumonitis, acute respiratory distress syndrome, allergic alveolitis), including fatalities, in patients receiving GIOTRIF for treatment of NSCLC. ILD-like adverse reactions 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). 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. Treatment with this medicinal product should be interrupted pending investigation of these symptoms. If ILD is diagnosed, GIOTRIF should be permanently discontinued and appropriate treatment initiated as necessary (see section 4.2).

Severe hepatic impairment
Hepatic failure, including fatalities, has been reported during treatment with this medicinal product 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. In the pivotal trials Grade 3 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations were observed in 2.4% (LUX-Lung-3) and 1.6% (LUX-Lung 8) of patients with normal baseline liver tests treated with 40 mg/day. In LUX-Lung-3 Grade 3 ALT/AST elevations were about 3.5 fold higher in patients with abnormal baseline liver tests. There were no Grade 3 ALT/AST elevations in patients with abnormal baseline liver tests in LUX-Lung 8 (see section 4.8). Dose interruption may become necessary in patients who experience worsening of liver function (see section 4.2). 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 should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. This medicinal product 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 4.8).

Left ventricular function
Left ventricular dysfunction has been associated with HER2 inhibition. Based on the available clinical trial data, there is no suggestion that this medicinal product causes an adverse reaction on cardiac contractility. However, this medicinal product 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 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 treatment interruption or discontinuation should be considered.

P-glycoprotein (P-gp) interactions
Concomitant treatment with strong inducers of P-gp may decrease exposure to afatinib (see section 4.5).

Lactose
This medicinal product contains lactose. Patients with rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with drug transport systems

Effects of P-gp and breast cancer resistance protein (BCRP) inhibitors on afatinib
In vitro studies have demonstrated that afatinib is a substrate of P-gp and BCRP. When the strong P-gp and BCRP inhibitor ritonavir (200 mg twice a day for 3 days) was administered 1 hour before a single dose of 20 mg GIOTRIF, exposure to afatinib increased by 48% (area under the curve ($AUC_{0-\infty}$)) and 39% (maximum plasma concentration (C_{max})). In contrast, when ritonavir was administered simultaneously or 6 hours after 40 mg GIOTRIF, the relative bioavailability of afatinib was 119% ($AUC_{0-\infty}$) and 104% (C_{max}) and 111% ($AUC_{0-\infty}$) and 105% (C_{max}), respectively. Therefore, it is recommended to administer strong P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) using staggered dosing, preferably 6 hours or 12 hours apart from GIOTRIF (see section 4.2).

Effects of P-gp inducers on afatinib
Pre-treatment with rifampicin (600 mg once daily 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. Strong P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's wort *(Hypericum perforatum)*) may decrease exposure to afatinib (see section 4.4).

Effects 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.

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 $AUC_{0-\infty}$. This medicinal product should be administered without food (see sections 4.2 and 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
As a precautionary measure, 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 1 month after the last dose.

Pregnancy
Mechanistically, all EGFR targeting medicinal products have the potential to cause foetal harm.
Animal studies with afatinib did not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Studies in animals have shown no signs of teratogenicity up to and including maternally lethal dose levels. Adverse changes were restricted to toxic dose levels. However, systemic exposures achieved in animals were either in a similar range or below the levels observed in patients (see section 5.3).

There are no or limited amount of data from the use of this medicinal product in pregnant women. The risk for humans is thus unknown. If used during pregnancy or if the patient becomes pregnant while or after receiving GIOTRIF, she should be informed of the potential hazard to the foetus.

Breast-feeding
Available pharmacokinetic data in animals have shown excretion of afatinib in milk (see section 5.3). Based on this, it is likely that afatinib is excreted in human milk. A risk to the breast-feeding child cannot be excluded. Mothers should be advised against breast-feeding while receiving this medicinal product.

Fertility
Fertility studies in humans have not been performed with afatinib. Available non-clinical toxicology data have shown effects on reproductive organs at higher doses. Therefore, an adverse effect of this medicinal product on human fertility cannot be excluded.

4.7 Effects on ability to drive and use machines

GIOTRIF has minor influence on the ability to drive and use machines. During treatment, ocular adverse reactions (conjunctivitis, dry eye, keratitis) have been reported in some patients (see section 4.8) which may affect patients ability to drive or use machines.

4.8 Undesirable effects

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 4.4) as well as stomatitis and paronychia (see also Table 3, 4 and 5). Overall, dose reduction (see section 4.2) 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 the 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 4.4).

Tabulated list of adverse reactions

Table 2 summarises the frequencies of ADRs from all NSCLC trials and from post-marketing experience with daily GIOTRIF doses of 40 mg or 50 mg 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 Aberrant eyelash growth	
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

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 section 4.4).

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 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

4.9 Overdose

Symptoms
The highest dose of afatinib 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 these doses were primarily dermatological (rash/acne) and gastrointestinal events (especially diarrhoea). Overdose in 2 healthy adolescents involving the ingestion of 360 mg each of afatinib (as part of a mixed drug ingestion) was associated with adverse events of nausea, vomiting, asthenia, dizziness, headache, abdominal pain and elevated amylase (< 1.5 times ULN). Both individuals recovered from these adverse events.

Treatment
There is no specific antidote for overdose with this medicinal product. In cases of suspected overdose, GIOTRIF should be withheld and supportive care initiated.

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 receptor mutations, and/or amplification, and/or receptor ligand overexpression contributes to the malignant phenotype. Mutation in EGFR defines a distinct molecular subtype of lung cancer.

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 tumours with common activating EGFR mutations (Del 19, L858R) and several less common EGFR mutations in exon 18 (G719X) and exon 21 (L861Q) are particularly sensitive to afatinib treatment in non-clinical and clinical settings. Limited non-clinical and/or clinical activity was observed in NSCLC tumours with insertion mutations in exon 20.

The acquisition of a secondary T790M 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. Other potential mechanisms of resistance to afatinib have been suggested preclinically and MET gene amplification has been observed clinically.

Clinical efficacy and safety

GIOTRIF in patients with Non-Small Cell Lung Cancer (NSCLC) with EGFR mutations

LUX-Lung 3
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. Patients 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 were randomised (2:1) to receive GIOTRIF 40 mg once daily or up to 6 cycles of pemetrexed/cisplatin. Among the patients randomised, 65% were female, the median age was 61 years, the baseline ECOG performance status was 0 (39%) or 1 (61%), 26% were Caucasian and 72% were Asian. 89% of patients had common EGFR mutations (Del 19 or L858R).

The primary endpoint was progression free survival (PFS) by independent review; the secondary endpoints included overall survival and objective response rate. At the time of the analysis, 14 Nov 2013, 176 patients (76.5%) in the afatinib arm and 70 patients (60.9%) in the chemotherapy arm experienced an event contributing to the PFS analysis, i.e. disease progression as determined by central independent review or death. The efficacy results are provided in Figure 1, Tables 6 and 7.

LUX-Lung 6

The efficacy and safety of GIOTRIF in Asian patients with Stage IIIB/IV EGFR mutation-positive locally advanced or metastatic adenocarcinoma of the lung was evaluated in a randomised, multicentre, open-label trial. Similar to LUX-Lung 3, patients with previously untreated NSCLC were screened for EGFR mutations using TheraScreen®: EGFR29 Mutation Kit (Qiagen Manchester Ltd). Among randomized patients, 65% were female, the median age was 58 years and all patients were of Asian ethnicity. Patients with common EGFR mutations accounted for 89% of the study population.

The primary endpoint was PFS as assessed by central independent review; secondary endpoints included OS and ORR.

Both trials demonstrated significant improvement in PFS of EGFR mutation positive patients treated with GIOTRIF compared to chemotherapy. The efficacy results are summarized in Figure 1 (LUX-Lung 3) and Tables 6 and 7 (LUX-Lung 3 and 6). Table 7 shows outcomes in the subgroups of patients with two common EGFR mutations – Del 19 and L858R.

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

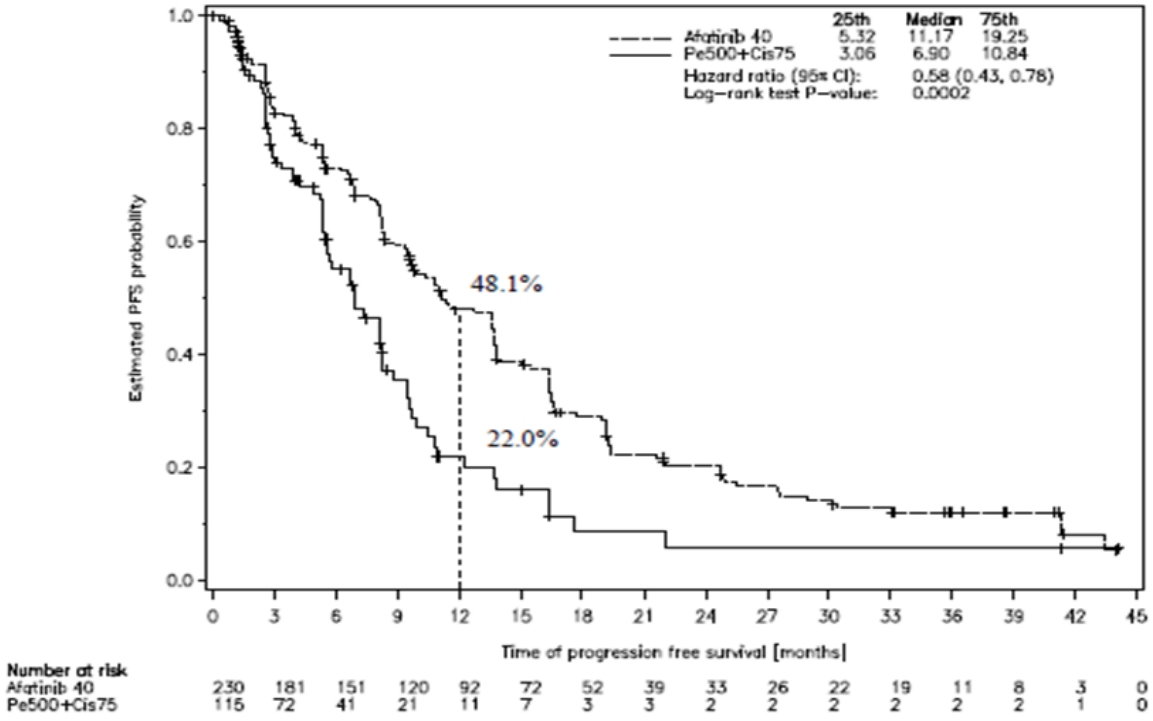


Table 6: Efficacy results of GIOTRIF vs. pemetrexed/cisplatin (LUX-Lung 3) gemcitabine/cisplatin (LUX-Lung 6) (Independent review)

	LUX-Lung 3		**LUX-Lung 6**	
	GIOTRIF (N=230)	**Pemetrexed/ Cisplatin** (N=115)	**GIOTRIF** (N=242)	**Gemcitabine/ Cisplatin** (N=122)
Progression-free survival Months (median)	11.2	6.9	11.0	5.6
Hazard Ratio (HR) (95%CI)	0.58 (0.43-0.78)		0.28 (0.20-0.39)	
p-value[1]	0.0002		<0.0001	
1-year PFS Rate	48.1%	22.0%	46.7%	2.1%
Objective Response Rate (CR+PR)[2]	56.5%	22.6%	67.8%	23.0%
Odds Ratio (OR) (95%CI)	4.80 (2.89-8.08)		7.57 (4.52-12.68)	
p-value[1]	<0.0001		<0.0001	
Overall Survival (OS) Months (median)	28.2	28.2	23.1	23.5
Hazard Ratio (HR) (95%CI)	0.88 (0.66-1.17)		0.93 (0.72-1.22)	
p-value[1]	0.3850		0.6137	

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

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

Table 7: PFS and OS efficacy results of GIOTRIF vs pemetrexed/cisplatin (LUX-Lung 3) gemcitabine/cisplatin (LUX-Lung 6) in the pre-defined EGFR mutation subgroups Del 19 and L858R (Independent review)

	LUX-Lung 3		**LUX-Lung 6**	
Del19	**GIOTRIF** (N=112)	**Pemetrexed/ Cisplatin** (N=57)	**GIOTRIF** (N=124)	**Gemcitabine/ Cisplatin** (N=62)
Progression-free survival Months (median)	13.8	5.6	13.1	5.6
Hazard Ratio (HR) (95%CI)	0.26 (0.17-0.42)		0.20 (0.13-0.33)	
p-value[1]	<0.0001		<0.0001	
Overall Survival (OS) Months (median)	33.3	21.1	31.4	18.4
Hazard Ratio (HR) (95%CI)	0.54 (0.36-0.79)		0.64 (0.44-0.94)	
p-value[1]	0.0015		0.0229	
L858R	**GIOTRIF** (N=91)	**Pemetrexed/ Cisplatin** (N=47)	**GIOTRIF** (N=92)	**Gemcitabine/ Cisplatin** (N=46)
Progression-free survival Months (median)	10.8	8.1	9.6	5.6
Hazard Ratio (HR) (95%CI)	0.75 (0.48-1.19)		0.31 (0.19-0.52)	
p-value[1]	0.2191		<0.0001	
Overall Survival (OS) Months (median)	27.6	40.3	19.6	24.3
Hazard Ratio (HR) (95%CI)	1.30 (0.80-2.11)		1.22 (0.81-1.83)	
p-value[1]	0.2919		0.3432	

[1] p-value for PFS/OS based on stratified log-rank test

In the pre-defined subgroup of common mutations (combined Del 19 and L858R) for GIOTRIF and chemotherapy, the median PFS was 13.6 months vs. 6.9 months (HR 0.48; 95% CI 0.35-0.66; p<0.0001; N=307) in LUX-Lung 3, and 11.0 months vs. 5.6 months (HR 0.24; 95% CI 0.17-0.35; p<0.0001; N=324) in LUX-Lung 6, respectively.

PFS benefit was accompanied by improvement in disease-related symptoms and delayed time to deterioration (see Table 8). Mean scores over time for overall quality of life, global health status and physical, role, cognitive, social and emotional functioning were significantly better for GIOTRIF.

Table 8: Symptom outcomes for GIOTRIF vs. chemotherapy in trials LUX-Lung 3 and LUX-Lung 6 (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
	LUX-Lung 6		
	Cough	**Dyspnoea**	**Pain**
% of patients improved [a]	76% vs. 55%; p=0.0003	71% vs. 48%; p<0.0001	65% vs. 47%; p=0.0017
Delay of median time to deterioration (months) [a,b]	31.1 vs. 10.3 HR 0.46; p=0.0001	7.7 vs. 1.7 HR 0.53; p<0.0001	6.9 vs. 3.4 HR 0.70; p=0.0220

[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 2
LUX-Lung 2 was a single arm Phase II trial in 129 EGFR TKI-naïve patients with stage IIIB or IV lung adenocarcinoma with EGFR mutations. Patients were enrolled in the first-line (N=61) or second-line setting (N=68) (i.e. after failure of 1 prior chemotherapy regimen). 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. Efficacy was similarly high in the group of patients who had received prior chemotherapy (N=68; ORR 57.4%; median PFS by independent review 8 months). The updated median OS for first- and second-line was 31.7 months and 23.6 months, respectively.

LUX-Lung 7
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 categorised 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 9.

Table 9: 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-naïve 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.

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

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. Randomization was stratified by race (Eastern Asian vs non Eastern Asian). The primary endpoint was PFS; OS was the key secondary endpoint. Other secondary endpoints included ORR, DCR, change in tumour size and HRQOL.
Among 795 patients randomized, the majority were males (84%), white (73%), current or former smokers (95%) with baseline performance status ECOG 1 (67%) and ECOG 0 (33%).
Second-line GIOTRIF significantly improved PFS and OS of patients with squamous NSCLC compared to

erlotinib. The efficacy results at the time of the primary analysis of OS including all randomized patients are summarized in Figure 2 and Table 10.

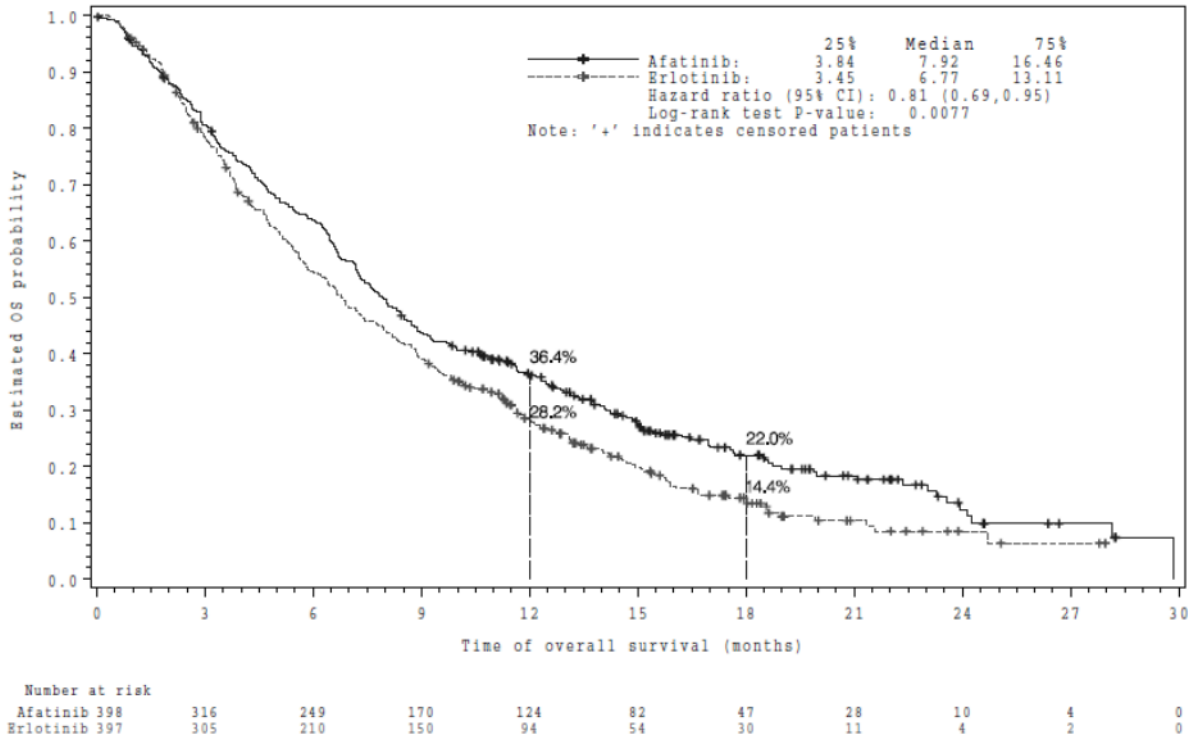
Table 10: Efficacy results for GIOTRIF vs erlotinib in LUX-Lung 8, based on primary analysis of OS, including all randomized patients

	GIOTRIF (N=398)	**Erlotinib (n=397)**	**Hazard Ratio/ Odds Ratio (95%CI)**	**p-value[2]**
PFS Months (median)	2.63	1.94	HR 0.81 (0.69, 0.96)	0.0103
OS Months (median)	7.92	6.77	HR 0.81 (0.69, 0.95)	0.0077
Alive at 12 months	36.4%	28.2%		
Alive at 18 months	22.0%	14.4%		
Objective Response Rate (CR+PR)[1]	5.5%	2.8%	OR 2.06 (0.98, 4.32)	0.0551
Duration of response Months (median)	7.29	3.71		

[1]CR=complete response; PR=partial response
[2]p-value for PFS/OS based on stratified log-rank test; p-value for Objective Response Rate based on logistic regression

The overall survival hazard ratio in patients < 65 years of age was 0.68 (95% CI 0.55, 0.85) and in patients 65 years of age and older it was 0.95 (95% CI 0.76, 1.19).

Figure 2: Kaplan-Meier Curve 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

Efficacy in EGFR-negative tumours has not been established.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of trials with this medicinal product in all subsets of the paediatric population in NSCLC indications (see section 4.2 for information on paediatric use). However, paediatric development was conducted in paediatric patients with other conditions.

A Phase I/II open-label, dose escalation, multicentre trial evaluated the safety and efficacy of GIOTRIF in paediatric patients aged 2 to less than 18 years with recurrent/refractory neuroectodermal tumours, rhabdomyosarcoma and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology. A total of 17 patients were treated in the dose finding part of the trial. In the maximum tolerated dose (MTD) expansion part of the trial, 39 patients selected by biomarkers for ErbB pathway deregulation received GIOTRIF at a dose of 18 mg/m²/day. In this expansion part, no objective responses were observed in 38 patients, including 6 patients with refractory high grade glioma (HGG), 4 patients with diffuse intrinsic pontine glioma (DIPG), 8 patients with ependymoma and 20 patients with other histologies. One patient with a neural-glial tumour of the brain with a CLIP2-EGFR gene fusion had a confirmed partial response (see section 4.2 for information on paediatric use). The adverse reaction profile of GIOTRIF in paediatric patients was consistent with the safety profile seen in adults.

5.2 Pharmacokinetic properties

Absorption
Following oral administration of GIOTRIF, C_{max} of afatinib were observed approximately 2 to 5 hours post dose. C_{max} and $AUC_{0-\infty}$ values increased slightly more than proportionally 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 to 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 4.2 and 4.5).

Distribution
In vitro binding of afatinib to human plasma proteins is approximately 95%. Afatinib binds to proteins both non-covalently (traditional protein binding) and covalently.

Biotransformation
Enzyme-catalyzed metabolic reactions play a negligible role for afatinib *in vivo*. Covalent adducts to proteins were the major circulating metabolites of afatinib.

Elimination
In humans, excretion of afatinib is primarily via the faeces. 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. Afatinib is eliminated with an effective half-life of

approximately 37 hours. Thus, steady state plasma concentrations of afatinib were achieved within 8 days of multiple dosing of afatinib resulting in an accumulation of 2.77-fold ($AUC_{0-\infty}$) and 2.11-fold (C_{max}). In patients treated with afatinib for more than 6 months a terminal half-life of 344 h was estimated.

Special populations

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 "Population pharmacokinetic analysis in special populations" below and section 4.2). 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 "Population pharmacokinetic analysis in special populations" below). No starting dose adjustments appear necessary in patients with mild or moderate hepatic impairment (see section 4.2). The pharmacokinetics of afatinib have not been studied in subjects with severe (Child Pugh C) hepatic dysfunction (see section 4.4).

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 was considered necessary for any of the following covariates tested.

Age
No significant impact of age (range: 28 years - 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 (2.5^{th} percentile) and decreased by 22% for a 95 kg patient (97.5^{th} 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
Race had no effect on the pharmacokinetics of afatinib based on a population pharmacokinetic analysis, including patients of Asian, White, and Black racial groups. Data on Black racial groups was limited.

Renal impairment
Exposure to afatinib moderately increased with lowering of the creatinine clearance (CrCL, calculated according to Cockcroft Gault), i.e. for a patient with a CrCL of 60 mL/min 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 mL/min 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. There was limited data available for moderate and severe hepatic impairment.

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 (limited data), or presence of liver metastases had no significant impact on the pharmacokinetics of afatinib.

Paediatric population
After administration of 18 mg/m2 afatinib, the steady-state exposure (AUC and C_{max}) in paediatric patients aged 2 to less than 18 years was comparable to that observed in adults given 40-50 mg afatinib (see also section 4.2 for information on paediatric use).

Other information on drug-drug interactions

Interactions with drug uptake transport systems
In vitro data indicated that drug-drug interactions with afatinib due to inhibition of OATP 1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, and OCT3 transporters are considered unlikely.

Interactions with Cytochrome P450 (CYP) enzymes
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. Afatinib is not an inhibitor or an inducer of CYP enzymes. Therefore, this medicinal product is unlikely to interact with other medicines that modulate or are metabolised by CYP enzymes.

Effect of UDP-glucuronosyltransferase 1A1 (UGT1A1) inhibition on afatinib
In vitro data indicated that drug-drug interactions with afatinib due to inhibition of UGT1A1 are considered unlikely.

5.3 Preclinical safety data

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, all EGFR targeting medicinal products including GIOTRIF have the potential to cause foetal harm. The embryo-foetal development studies performed on afatinib revealed no indication of teratogenicity. 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 in the breast milk of the dams.

A fertility study in male and female rats up to the maximum tolerated dose revealed no significant impact on fertility. The total systemic exposure (AUC_{0-24}) 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 up to the maximum tolerated doses revealed no significant impact on pre-/postnatal development. The highest total systemic exposure (AUC_{0-24}) in female rats was less than that observed in patients (0.23 times).

Phototoxicity
An *in vitro* 3T3 test showed that afatinib may have phototoxicity potential.

Carcinogenicity
Carcinogenicity studies have not been conducted with GIOTRIF.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose, monohydrate
Cellulose, microcrystalline
Crospovidone
Magnesium stearate
Silica, colloidal anhydrous

Film-coating

GIOTRIF 20 mg
Hypromellose 2910
Titanium dioxide
Talc
Macrogol 400
Polysorbate 80

GIOTRIF 30 mg
Hypromellose 2910
Talc
Macrogol 400
Titanium dioxide
Indigo carmine aluminium lake
Polysorbate 80

GIOTRIF 40 mg
Hypromellose 2910
Titanium dioxide
Talc
Macrogol 400
Polysorbate 80
Indigo carmine aluminium lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25^{0}C. Store in the original package in order to protect from moisture and light. Following first opening of the aluminium pouch the blister tablets can be used within 14 days.

6.5 Nature and contents of container

PVC/PVDC perforated unit dose blister. Each blister is packed together with a desiccant sachet in a laminated aluminium pouch and contains 7 x 1 film-coated tablets. Pack sizes of 7 x 1, 14 x 1 or 28 x 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Boehringer Ingelheim Pharma GmbH & CO. KG
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Germany

8. MARKETING AUTHORISATION HOLDER

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Medinat Ha-Yehudim 89 St.
P.O. Box 4124
Herzliya Pituach 4676672

9. MARKETING AUTHORISATION NUMBERS

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Giotrif 30 mg	151-48-33986-00
Giotrif 40 mg	151-49-33987-00

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