

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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

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 118 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 176 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 235 mg lactose (as monohydrate).

GIOTRIF 50 mg film-coated tablets

One film-coated tablet contains 50 mg afatinib (as dimaleate).

Excipient with known effect: 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 (tablet).

GIOTRIF 20 mg film-coated tablets

White to 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 film-coated tablets

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 film-coated tablets

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.

GIOTRIF 50 mg film-coated tablets

Dark blue, oval, biconvex film-coated tablet debossed with the code “T50” 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).

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. 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 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 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.

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.

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, the Lapp 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)
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	
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 erythrodysesthesia syndrome		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

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

NCI-CTC Grade	GIOTRIF (40 mg/day) N=229			Pemetrexed/ Cisplatin N=111		
	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
<i>Infections and infestations</i>						
Paronychia ¹	57.6	11.4	0	0	0	0
<i>Metabolism and nutrition disorders</i>						
Decreased appetite	20.5	3.1	0	53.2	2.7	0
<i>Respiratory, thoracic and mediastinal disorders</i>						
Epistaxis	13.1	0	0	0.9	0.9	0
<i>Gastrointestinal disorders</i>						
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
<i>Skin and subcutaneous tissue disorders</i>						
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
<i>Investigations</i>						
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		
	Any Grade	3	4	Any Grade	3	4
NCI-CTC Grade	%	%	%	%	%	%
MedDRA Preferred Term	%	%	%	%	%	%
<i>Infections and infestations</i>						
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
<i>Metabolism and nutrition disorders</i>						
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
<i>Respiratory, thoracic and mediastinal disorders</i>						
Rhinorrhoea ⁴	19.4	0	0	7.5	0	0
Epistaxis	18.1	0	0	8.8	0	0
<i>Gastrointestinal disorders</i>						
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
<i>Hepatobiliary disorders</i>						
Alanine aminotransferase increased	11.3	0	0	27.7	8.8	0.6
<i>Skin and subcutaneous tissue disorders</i>						
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
<i>General disorders and administration site conditions</i>						
Pyrexia	13.8	0	0	6.3	0	0
<i>Investigations</i>						
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	%	%	%	%	%	%
<i>Infections and infestations</i>						
Paronychia ¹	11.0	0.5	0	5.1	0.3	0
<i>Metabolism and nutrition disorders</i>						
Decreased appetite	24.7	3.1	0	26.1	2.0	0
<i>Gastrointestinal disorders</i>						
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
<i>Skin and subcutaneous tissue disorders</i>						
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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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: L01XE13.

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.

Afatinib retains significant anti-tumour activity in NSCLC cell lines *in vitro* and/or tumour models *in vivo* (xenografts or transgenic models) driven by mutant EGFR isoforms known to be resistant to the reversible EGFR inhibitors erlotinib and gefitinib such as T790M or T854A. Clinically, activity in tumours harbouring the T790M mutation in exon 20 has also been shown. Limited non-clinical and/or clinical activity was observed in NSCLC tumours with insertion mutations in exon 20.

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)

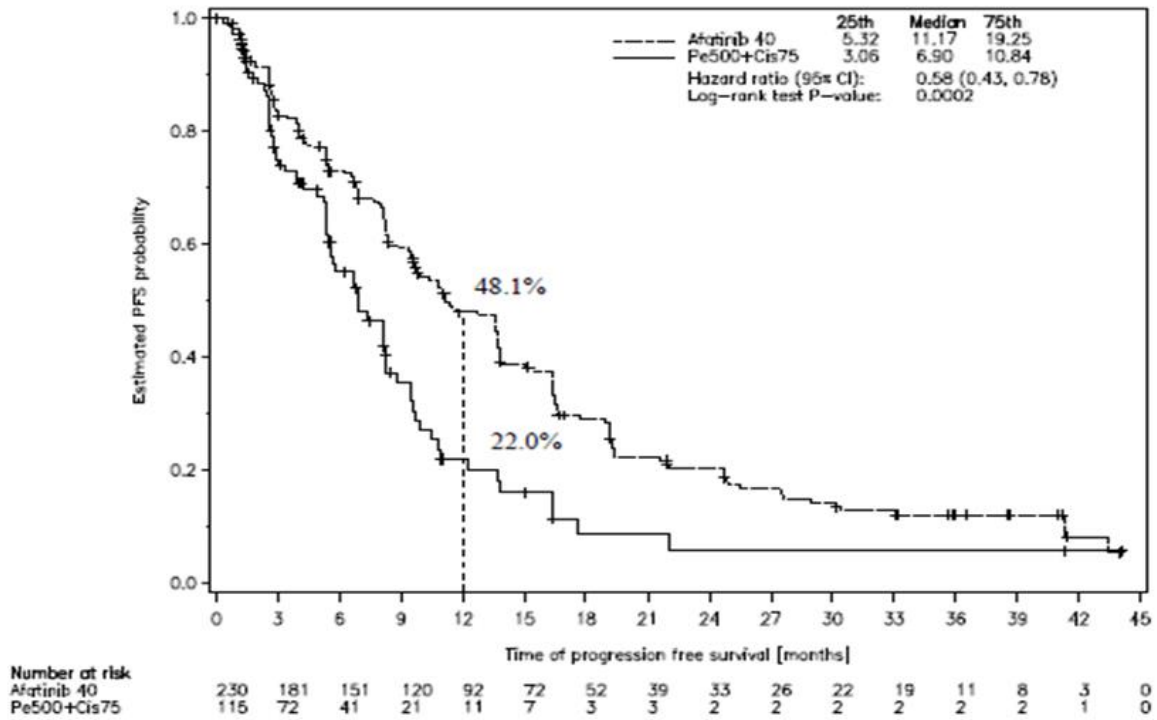


Table 6: Efficacy results of GIOTRIF vs. pemetrexed/cisplatin (LUX-Lung 3) gemcitabine/cisplatin (LUX-Lung 6) (Independent review)

	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	
	GIOTRIF (N=112)	Pemetrexed/ Cisplatin (N=57)	GIOTRIF (N=124)	Gemcitabine/ Cisplatin (N=62)
Del19				
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				
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-value²
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

¹OS 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

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

³CR=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.

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

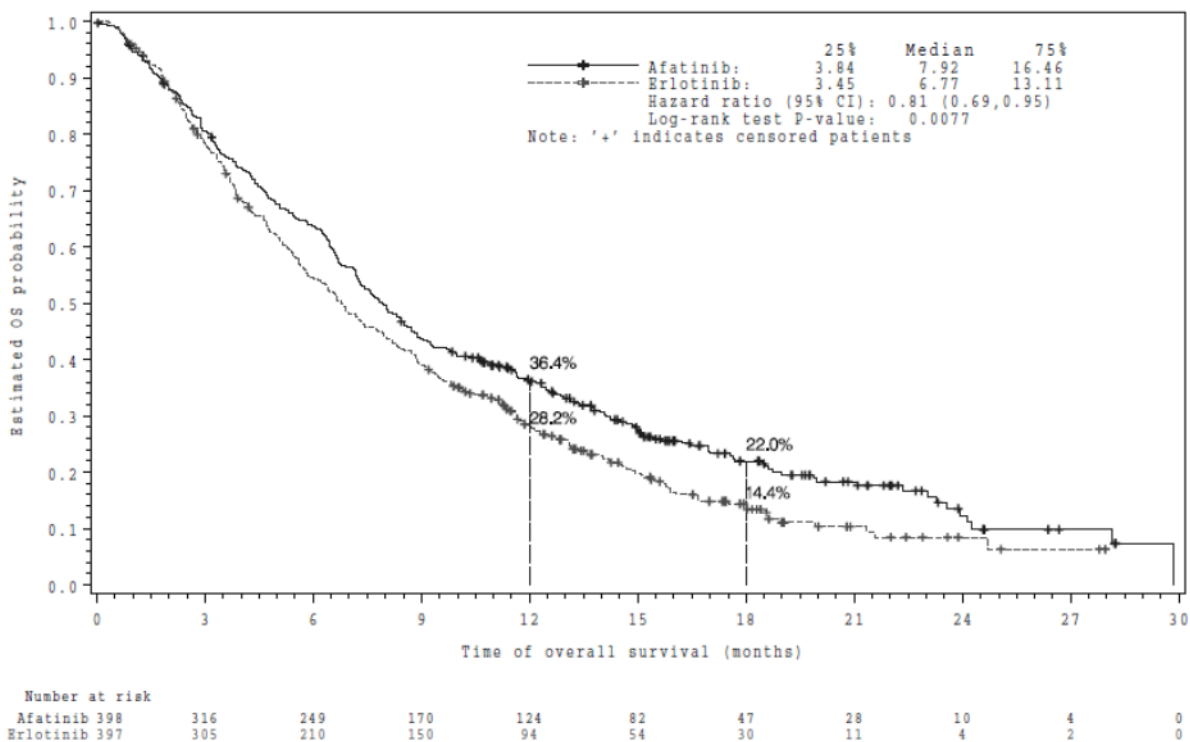
	GIOTRIF (N=398)	Erlotinib (n=397)	Hazard Ratio/ Odds Ratio (95%CI)	p-value²
PFS Months (median)	2.63	1.94	HR 0.81 (0.69, 0.96)	0.0103
OS Months (median)	7.92	6.77	HR 0.81 (0.69, 0.95)	0.0077
Alive at 12 months	36.4%	28.2%		
Alive at 18 months	22.0%	14.4%		
Objective Response Rate (CR+PR)¹	5.5%	2.8%	OR 2.06 (0.98, 4.32)	0.0551
Duration of response Months (median)	7.29	3.71		

¹CR=complete response; PR=partial response

²p-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).

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 (2.5th 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

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.

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 OATB1B1, 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 (AUC₀₋₂₄) 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 (AUC₀₋₂₄) 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 (E460)
Silica, colloidal anhydrous (E551)
Crospovidone type A
Magnesium stearate (E470b)

Film-coating

GIOTRIF 20 mg film-coated tablets

Hypromellose (E464)
Macrogol 400
Titanium dioxide (E171)
Talc (E553b)
Polysorbate 80 (E433)

GIOTRIF 30, 40 and 50 mg film-coated tablets

Hypromellose (E464)
Macrogol 400
Titanium dioxide (E171)
Talc (E553b)
Polysorbate 80 (E433)
Indigo carmine (E132) aluminium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture and light.

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. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

GIOTRIF 20 mg film-coated tablets

EU/1/13/879/001
EU/1/13/879/002
EU/1/13/879/003

GIOTRIF 30 mg film-coated tablets

EU/1/13/879/004
EU/1/13/879/005
EU/1/13/879/006

GIOTRIF 40 mg film-coated tablets

EU/1/13/879/007
EU/1/13/879/008
EU/1/13/879/009

GIOTRIF 50 mg film-coated tablets

EU/1/13/879/010
EU/1/13/879/011
EU/1/13/879/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 September 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETINGAUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim am Rhein
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products on “restricted” medical prescription, reserved for use in certain specialised areas (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (FOLDING BOX FOR BLISTER for 20 mg)

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 20 mg film-coated tablets
afatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg afatinib (as dimaleate).

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 x 1 film-coated tablets
14 x 1 film-coated tablets
28 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/879/001
EU/1/13/879/002
EU/1/13/879/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GIOTRIF 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number} [product code]

SN: {number} [serial number]

NN: {number} [national reimbursement number or other national number identifying the medicinal product]

MINIMUM PARTICULARS TO APPEAR ON ALUMINIUM POUCH

ALUMINIUM POUCH for 20 mg

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 20 mg film-coated tablets
afatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not open before use.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED BLISTER for 20 mg

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 20 mg tablets
afatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not open before use. *

* only printed on one empty blister unit; i.e. not printed on blister units containing actual tablets. This ensures that text is readable until last tablet of blister card is used.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (FOLDING BOX FOR BLISTER for 30 mg)

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 30 mg film-coated tablets
afatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 30 mg afatinib (as dimaleate).

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 x 1 film-coated tablets
14 x 1 film-coated tablets
28 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/879/004
EU/1/13/879/005
EU/1/13/879/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GIOTRIF 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number} [product code]

SN: {number} [serial number]

NN: {number} [national reimbursement number or other national number identifying the medicinal product]

MINIMUM PARTICULARS TO APPEAR ON ALUMINIUM POUCH

ALUMINIUM POUCH for 30 mg

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 30 mg film-coated tablets
afatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not open before use.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED BLISTER for 30 mg

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 30 mg tablets
afatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not open before use. *

* only printed on one empty blister unit; i.e. not printed on blister units containing actual tablets. This ensures that text is readable until last tablet of blister card is used.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (FOLDING BOX FOR BLISTER for 40 mg)

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 40 mg film-coated tablets
afatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg afatinib (as dimaleate).

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 x 1 film-coated tablets
14 x 1 film-coated tablets
28 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/879/007
EU/1/13/879/008
EU/1/13/879/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GIOTRIF 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number} [product code]

SN: {number} [serial number]

NN: {number} [national reimbursement number or other national number identifying the medicinal product]

MINIMUM PARTICULARS TO APPEAR ON ALUMINIUM POUCH

ALUMINIUM POUCH for 40 mg

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 40 mg film-coated tablets
afatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not open before use.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED BLISTER for 40 mg

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 40 mg tablets
afatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not open before use. *

* only printed on one empty blister unit; i.e. not printed on blister units containing actual tablets. This ensures that text is readable until last tablet of blister card is used.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (FOLDING BOX FOR BLISTER for 50 mg)

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 50 mg film-coated tablets
afatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg afatinib (as dimaleate).

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 x 1 film-coated tablets
14 x 1 film-coated tablets
28 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/879/010
EU/1/13/879/011
EU/1/13/879/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GIOTRIF 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number} [product code]

SN: {number} [serial number]

NN: {number} [national reimbursement number or other national number identifying the medicinal product]

MINIMUM PARTICULARS TO APPEAR ON ALUMINIUM POUCH

ALUMINIUM POUCH for 50 mg

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 50 mg film-coated tablets
afatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not open before use.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED BLISTER for 50 mg

1. NAME OF THE MEDICINAL PRODUCT

GIOTRIF 50 mg tablets
afatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not open before use. *

* only printed on one empty blister unit; i.e. not printed on blister units containing actual tablets. This ensures that text is readable until last tablet of blister card is used.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

GIOTRIF 20 mg film-coated tablets

afatinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If any of these side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

What is in this leaflet

1. What GIOTRIF is and what it is used for
2. What you need to know before you take GIOTRIF
3. How to take GIOTRIF
4. Possible side effects
5. How to store GIOTRIF
6. Contents of the pack and other information

1. What GIOTRIF is and what it is used for

GIOTRIF is a medicine which contains the active substance afatinib. It works by blocking the activity of a group of proteins called the ErbB family (including EGFR [epidermal growth factor receptor or ErbB1], HER2 [ErbB2], ErbB3 and ErbB4). These proteins are involved in the growth and spread of cancer cells, and can be affected by changes (mutations) in the genes that produce them. By blocking the activity of these proteins this medicine can inhibit growth and spread of cancer cells.

This medicine is used on its own to treat adult patients with a specific type of cancer of the lung (non-small cell lung cancer):

- that is identified by a change (mutation) in the gene for EGFR. GIOTRIF can be prescribed to you as your first treatment or if prior chemotherapy treatment has been insufficient.
- of squamous type if prior chemotherapy treatment has been insufficient.

2. What you need to know before you take GIOTRIF

Do not take GIOTRIF

- if you are allergic to afatinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking this medicine:

- if you are female, have a low body weight of less than 50 kg or have kidney problems. If any of these apply to you, your doctor may monitor you more closely as the side effects may be more pronounced.
- if you have a history of lung inflammation (interstitial lung disease).

- if you have liver problems. Your doctor may do some liver tests. Treatment with this medicine is not recommended if you have a severe liver disease.
- if you have a history of eye problems such as severe dry eyes, inflammation of the transparent layer at the front of the eye (cornea) or ulcers involving the outer part of the eye, or if you use contact lenses.
- if you have a history of heart problems. Your doctor may want to monitor you more closely.

Inform your doctor immediately while taking this medicine:

- if you develop diarrhoea. Treatment at the first signs of diarrhoea is important.
- if you develop skin rash. Early treatment of skin rash is important.
- if you develop new or sudden worsening of shortness of breath, possibly with a cough or fever. These could be symptoms of an inflammation of the lungs (interstitial lung disease) and can be life-threatening.
- if you develop acute or worsening redness and pain in the eye, increased eye watering, blurred vision and/or sensitivity to light. You may need urgent treatment.

See also Possible side effects in section 4.

Children and adolescents

GIOTRIF has not been studied in children or adolescents. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and GIOTRIF

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including herbal medicines and medicines obtained without a prescription.

In particular, if taken before GIOTRIF, the following medicines may increase the blood levels of GIOTRIF and therefore the risk of side effects. They should therefore be taken as far apart in time as possible from GIOTRIF. This means preferably 6 hours (for medicines taken twice daily) or 12 hours (for medicines taken once daily) apart from GIOTRIF:

- Ritonavir, ketoconazole (except in shampoo), itraconazole, erythromycin, nelfinavir, saquinavir - used to treat different kinds of infections.
- Verapamil, quinidine, amiodarone - used to treat heart conditions.
- Cyclosporine A, tacrolimus - medicines that affect your immune system.

The following medicines may reduce the effectiveness of GIOTRIF:

- Carbamazepine, phenytoin, phenobarbital - used to treat seizures.
- St. John's wort (*Hypericum perforatum*), a herbal medicine to treat depression.
- Rifampicin, an antibiotic used to treat tuberculosis.

Ask your doctor if you are unsure of when to take these medicines.

GIOTRIF may increase the blood levels of other medicines including but not limited to:

- Sulfasalazine, used to treat inflammation/infection.
- Rosuvastatin, used for lowering cholesterol.

Tell your doctor before taking these medicines together with GIOTRIF.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

You should avoid becoming pregnant while taking this medicine. If you could become pregnant, you should use adequate birth control methods during treatment and for at least 1 month after taking the last dose of this medicine. This is because there may be a risk that an unborn baby is harmed.

If you become pregnant while receiving this medicine, you should immediately inform your doctor. Your doctor will decide with you whether treatment should be continued or not.

If you plan to become pregnant after taking the last dose of this medicine, you should ask your doctor for advice as your body may not have fully eliminated this medicine.

Breast-feeding

Do not breast-feed while taking this medicine as a risk to the breast-fed child cannot be excluded.

Driving and using machines

If you experience treatment-related symptoms affecting your eye sight (e.g. redness and/or irritation of the eye, dry eye, tearing, light-sensitivity) or your ability to concentrate and react, it is recommended that you do not drive or use machines until the side effect disappears (see section 4 Possible side effects).

GIOTRIF contains lactose

This medicine contains a sugar called lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take GIOTRIF

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage

The recommended dose is 40 mg each day.

Your doctor may adjust (increase or decrease) your dose depending on how well you tolerate this medicine.

When to take GIOTRIF

- It is important to take this medicine without food
- Take this medicine at least 1 hour before eating, or
- If you have already eaten, wait at least 3 hours before taking this medicine.
- Take this medicine once daily about the same time each day. This makes it easier to remember to take this medicine.
- Do not break, chew or crush the tablet.
- Swallow the tablet whole with a glass of still water.

GIOTRIF is to be taken by mouth. If you have difficulties swallowing the tablet, dissolve it in a glass of still water. No other liquids should be used. Drop the tablet into the water without crushing it, and occasionally stir for up to 15 min until the tablet is broken up into very small particles. Drink the liquid straight away. Then fill the glass again with water and drink it to make sure all medicine is taken.

If you are not able to swallow and have a gastric tube your doctor might suggest that the medicine is given to you via the tube.

If you take more GIOTRIF than you should

Contact your doctor or pharmacist immediately. You may experience increased side effects and your doctor may interrupt your treatment and provide supportive care.

If you forget to take GIOTRIF

- If your next scheduled dose is more than 8 hours away, take the missed dose as soon as you remember.
- If your next scheduled dose is due within 8 hours, skip the missed dose and take your next dose at the usual time. Then carry on taking your tablets at regular times as usual.

Do not take a double dose (two tablets instead of one at the same time) to make up for a missed dose.

If you stop taking GIOTRIF

Do not stop taking this medicine without first consulting your doctor. It is important to take this medicine every day, as long as your doctor prescribes it for you. If you do not take this medicine as prescribed by your doctor your cancer may grow again.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, GIOTRIF can cause side effects, although not everybody gets them.

Contact your doctor as soon as possible if you suffer from any of the serious side effects listed below. In some cases your doctor may need to interrupt treatment and reduce your dose or stop treatment:

- **Diarrhoea** (very common, may affect more than 1 in 10 people).
Diarrhoea lasting more than 2 days or more severe diarrhoea may lead to fluid loss (common, may affect up to 1 in 10 people), low blood potassium (common) and worsening kidney function (common). Diarrhoea can be treated. At the first signs of diarrhoea drink plenty of fluids. Contact your doctor immediately and start appropriate antidiarrhoeal treatment as soon as possible. You should have antidiarrhoeal medicine available prior to taking GIOTRIF.
- **Skin rash** (very common).
It is important to treat the rash early. Tell your doctor if a rash starts. If treatment for rash is not working and the rash is getting more severe (for example, you have peeling or blistering of the skin) you should notify your doctor immediately, since your doctor may decide to stop your treatment with GIOTRIF. Rash may occur or worsen in areas exposed to sun. Sun protection with protective clothing and sunscreen is recommended.
- **Inflammation of the lungs** (uncommon, may affect up to 1 in 100 people) called “interstitial lung disease”.
Tell your doctor immediately if you develop new or sudden worsening of shortness of breath, possibly with a cough or fever.
- **Eye irritation or inflammation**
Eye irritation or inflammation may occur (conjunctivitis/keratoconjunctivitis occurs commonly and keratitis uncommonly). Tell your doctor if you have sudden or worsening of eye symptoms such as pain or redness or dry eye.

If you experience any of the symptoms above, contact your doctor as soon as possible.

The following other side effects have also been reported:

Very common side effects (may affect more than 1 in 10 people):

- Mouth sores and inflammation
- Nail infection
- Decreased appetite
- Bleeding from the nose
- Nausea
- Vomiting

Common side effects (may affect up to 1 in 10 people):

- Pain, redness, swelling or peeling of the skin of your hands and feet
- Increased levels of the liver enzymes (aspartate aminotransferase and alanine aminotransferase) in blood tests.

- Inflammation of the lining of the bladder with burning sensations during urination and frequent, urgent need to urinate (cystitis)
- Abnormal taste sensations (dysgeusia)
- Stomach pain, indigestion, heartburn
- Lip inflammation
- Decreased weight
- Runny nose
- Muscle spasms
- Fever

Uncommon side effects (may affect up to 1 in 100 people):

- Inflammation of the pancreas (pancreatitis)

Rare side effects (may affect up to 1 in 1,000 people):

- Severe blistering or peeling of skin (suggestive of Stevens-Johnson syndrome and toxic epidermal necrolysis)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GIOTRIF

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, the pouch and the blister after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture and light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What GIOTRIF contains

- The active substance is afatinib. Each film-coated tablet contains 20 mg of afatinib (as dimaleate).
- The other ingredients are lactose monohydrate, microcrystalline cellulose (E460), colloidal anhydrous silica (E551), crospovidone type A, magnesium stearate (E470b), hypromellose (E464), macrogol 400, titanium dioxide (E171), talc (E553b), polysorbate 80 (E433).

What GIOTRIF looks like and contents of the pack

GIOTRIF 20 mg film-coated tablets are white to yellowish and round shaped. They are debossed with the code “T20” on one side and the Boehringer Ingelheim company logo on the other.

GIOTRIF film-coated tablets are available in packs containing 1, 2 or 4 perforated unit dose blisters. Each blister contains 7 x 1 film-coated tablets and is packed together with a desiccant sachet in an aluminium pouch.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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

Manufacturer

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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United Kingdom

Boehringer Ingelheim Ltd.
Tel: +44 1344 424 600

This leaflet was last approved in {MM/YYYY}

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

Package leaflet: Information for the patient

GIOTRIF 30 mg film-coated tablets

afatinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If any of these side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

What is in this leaflet

1. What GIOTRIF is and what it is used for
2. What you need to know before you take GIOTRIF
3. How to take GIOTRIF
4. Possible side effects
5. How to store GIOTRIF
6. Contents of the pack and other information

1. What GIOTRIF is and what it is used for

GIOTRIF is a medicine which contains the active substance afatinib. It works by blocking the activity of a group of proteins called the ErbB family (including EGFR [epidermal growth factor receptor or ErbB1], HER2 [ErbB2], ErbB3 and ErbB4). These proteins are involved in the growth and spread of cancer cells, and can be affected by changes (mutations) in the genes that produce them. By blocking the activity of these proteins this medicine can inhibit growth and spread of cancer cells.

This medicine is used on its own to treat adult patients with a specific type of cancer of the lung (non-small cell lung cancer):

- that is identified by a change (mutation) in the gene for EGFR. GIOTRIF can be prescribed to you as your first treatment or if prior chemotherapy treatment has been insufficient.
- of squamous type if prior chemotherapy treatment has been insufficient.

2. What you need to know before you take GIOTRIF

Do not take GIOTRIF

- if you are allergic to afatinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking this medicine:

- if you are female, have a low body weight of less than 50 kg or have kidney problems. If any of these apply to you, your doctor may monitor you more closely as the side effects may be more pronounced.
- if you have a history of lung inflammation (interstitial lung disease).

- if you have liver problems. Your doctor may do some liver tests. Treatment with this medicine is not recommended if you have a severe liver disease.
- if you have a history of eye problems such as severe dry eyes, inflammation of the transparent layer at the front of the eye (cornea) or ulcers involving the outer part of the eye, or if you use contact lenses.
- if you have a history of heart problems. Your doctor may want to monitor you more closely.

Inform your doctor immediately while taking this medicine:

- if you develop diarrhoea. Treatment at the first signs of diarrhoea is important.
- if you develop skin rash. Early treatment of skin rash is important.
- if you develop new or sudden worsening of shortness of breath, possibly with a cough or fever. These could be symptoms of an inflammation of the lungs (interstitial lung disease) and can be life-threatening.
- if you develop acute or worsening redness and pain in the eye, increased eye watering, blurred vision and/or sensitivity to light. You may need urgent treatment.

See also Possible side effects in section 4.

Children and adolescents

GIOTRIF has not been studied in children or adolescents. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and GIOTRIF

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including herbal medicines and medicines obtained without a prescription.

In particular, if taken before GIOTRIF, the following medicines may increase the blood levels of GIOTRIF and therefore the risk of side effects. They should therefore be taken as far apart in time as possible from GIOTRIF. This means preferably 6 hours (for medicines taken twice daily) or 12 hours (for medicines taken once daily) apart from GIOTRIF:

- Ritonavir, ketoconazole (except in shampoo), itraconazole, erythromycin, nelfinavir, saquinavir - used to treat different kinds of infections.
- Verapamil, quinidine, amiodarone - used to treat heart conditions.
- Cyclosporine A, tacrolimus - medicines that affect your immune system.

The following medicines may reduce the effectiveness of GIOTRIF:

- Carbamazepine, phenytoin, phenobarbital - used to treat seizures.
- St. John's wort (*Hypericum perforatum*), a herbal medicine to treat depression.
- Rifampicin, an antibiotic used to treat tuberculosis.

Ask your doctor if you are unsure of when to take these medicines.

GIOTRIF may increase the blood levels of other medicines including but not limited to:

- Sulfasalazine, used to treat inflammation/infection.
- Rosuvastatin, used for lowering cholesterol.

Tell your doctor before taking these medicines together with GIOTRIF.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

You should avoid becoming pregnant while taking this medicine. If you could become pregnant, you should use adequate birth control methods during treatment and for at least 1 month after taking the last dose of this medicine. This is because there may be a risk that an unborn baby is harmed.

If you become pregnant while receiving this medicine, you should immediately inform your doctor. Your doctor will decide with you whether treatment should be continued or not.

If you plan to become pregnant after taking the last dose of this medicine, you should ask your doctor for advice as your body may not have fully eliminated this medicine.

Breast-feeding

Do not breast-feed while taking this medicine as a risk to the breast-fed child cannot be excluded.

Driving and using machines

If you experience treatment-related symptoms affecting your eye sight (e.g. redness and/or irritation of the eye, dry eye, tearing, light-sensitivity) or your ability to concentrate and react, it is recommended that you do not drive or use machines until the side effect disappears (see section 4 Possible side effects).

GIOTRIF contains lactose

This medicine contains a sugar called lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take GIOTRIF

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage

The recommended dose is 40 mg each day.

Your doctor may adjust (increase or decrease) your dose depending on how well you tolerate this medicine.

When to take GIOTRIF

- It is important to take this medicine without food
- Take this medicine at least 1 hour before eating, or
- If you have already eaten, wait at least 3 hours before taking this medicine.
- Take this medicine once daily about the same time each day. This makes it easier to remember to take this medicine.
- Do not break, chew or crush the tablet.
- Swallow the tablet whole with a glass of still water.

GIOTRIF is to be taken by mouth. If you have difficulties swallowing the tablet, dissolve it in a glass of still water. No other liquids should be used. Drop the tablet into the water without crushing it, and occasionally stir for up to 15 min until the tablet is broken up into very small particles. Drink the liquid straight away. Then fill the glass again with water and drink it to make sure all medicine is taken.

If you are not able to swallow and have a gastric tube your doctor might suggest that the medicine is given to you via the tube.

If you take more GIOTRIF than you should

Contact your doctor or pharmacist immediately. You may experience increased side effects and your doctor may interrupt your treatment and provide supportive care.

If you forget to take GIOTRIF

- If your next scheduled dose is more than 8 hours away, take the missed dose as soon as you remember.
- If your next scheduled dose is due within 8 hours, skip the missed dose and take your next dose at the usual time. Then carry on taking your tablets at regular times as usual.

Do not take a double dose (two tablets instead of one at the same time) to make up for a missed dose.

If you stop taking GIOTRIF

Do not stop taking this medicine without first consulting your doctor. It is important to take this medicine every day, as long as your doctor prescribes it for you. If you do not take this medicine as prescribed by your doctor your cancer may grow again.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, GIOTRIF can cause side effects, although not everybody gets them.

Contact your doctor as soon as possible if you suffer from any of the serious side effects listed below. In some cases your doctor may need to interrupt treatment and reduce your dose or stop treatment:

- **Diarrhoea** (very common, may affect more than 1 in 10 people).
Diarrhoea lasting more than 2 days or more severe diarrhoea may lead to fluid loss (common, may affect up to 1 in 10 people), low blood potassium (common) and worsening kidney function (common). Diarrhoea can be treated. At the first signs of diarrhoea drink plenty of fluids. Contact your doctor immediately and start appropriate antidiarrhoeal treatment as soon as possible. You should have antidiarrhoeal medicine available prior to taking GIOTRIF.
- **Skin rash** (very common).
It is important to treat the rash early. Tell your doctor if a rash starts. If treatment for rash is not working and the rash is getting more severe (for example, you have peeling or blistering of the skin) you should notify your doctor immediately, since your doctor may decide to stop your treatment with GIOTRIF. Rash may occur or worsen in areas exposed to sun. Sun protection with protective clothing and sunscreen is recommended.
- **Inflammation of the lungs** (uncommon, may affect up to 1 in 100 people) called “interstitial lung disease”.
Tell your doctor immediately if you develop new or sudden worsening of shortness of breath, possibly with a cough or fever.
- **Eye irritation or inflammation**
Eye irritation or inflammation may occur (conjunctivitis/keratoconjunctivitis occurs commonly and keratitis uncommonly). Tell your doctor if you have sudden or worsening of eye symptoms such as pain or redness or dry eye.

If you experience any of the symptoms above, contact your doctor as soon as possible.

The following other side effects have also been reported:

Very common side effects (may affect more than 1 in 10 people):

- Mouth sores and inflammation
- Nail infection
- Decreased appetite
- Bleeding from the nose
- Nausea
- Vomiting

Common side effects (may affect up to 1 in 10 people):

- Pain, redness, swelling or peeling of the skin of your hands and feet
- Increased levels of the liver enzymes (aspartate aminotransferase and alanine aminotransferase) in blood tests.

- Inflammation of the lining of the bladder with burning sensations during urination and frequent, urgent need to urinate (cystitis)
- Abnormal taste sensations (dysgeusia)
- Stomach pain, indigestion, heartburn
- Lip inflammation
- Decreased weight
- Runny nose
- Muscle spasms
- Fever

Uncommon side effects (may affect up to 1 in 100 people):

- Inflammation of the pancreas (pancreatitis)

Rare side effects (may affect up to 1 in 1,000 people):

- Severe blistering or peeling of skin (suggestive of Stevens-Johnson syndrome and toxic epidermal necrolysis)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GIOTRIF

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, the pouch and the blister after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture and light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What GIOTRIF contains

- The active substance is afatinib. Each film-coated tablet contains 30 mg of afatinib (as dimaleate).
- The other ingredients are lactose monohydrate, microcrystalline cellulose (E460), colloidal anhydrous silica (E551), crospovidone type A, magnesium stearate (E470b), hypromellose (E464), macrogol 400, titanium dioxide (E171), talc (E553b), polysorbate 80 (E433), indigo carmine (E132) aluminium hydroxide.

What GIOTRIF looks like and contents of the pack

GIOTRIF 30 mg film-coated tablets are dark blue and round shaped. They are debossed with the code “T30” on one side and the Boehringer Ingelheim company logo on the other.

GIOTRIF film-coated tablets are available in packs containing 1, 2 or 4 perforated unit dose blisters. Each blister contains 7 x 1 film-coated tablets and is packed together with a desiccant sachet in an aluminium pouch.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last approved in {MM/YYYY}

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

Package leaflet: Information for the patient

GIOTRIF 40 mg film-coated tablets

afatinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If any of these side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

What is in this leaflet

1. What GIOTRIF is and what it is used for
2. What you need to know before you take GIOTRIF
3. How to take GIOTRIF
4. Possible side effects
5. How to store GIOTRIF
6. Contents of the pack and other information

1. What GIOTRIF is and what it is used for

GIOTRIF is a medicine which contains the active substance afatinib. It works by blocking the activity of a group of proteins called the ErbB family (including EGFR [epidermal growth factor receptor or ErbB1], HER2 [ErbB2], ErbB3 and ErbB4). These proteins are involved in the growth and spread of cancer cells, and can be affected by changes (mutations) in the genes that produce them. By blocking the activity of these proteins this medicine can inhibit growth and spread of cancer cells.

This medicine is used on its own to treat adult patients with a specific type of cancer of the lung (non-small cell lung cancer):

- that is identified by a change (mutation) in the gene for EGFR. GIOTRIF can be prescribed to you as your first treatment or if prior chemotherapy treatment has been insufficient.
- of squamous type if prior chemotherapy treatment has been insufficient.

2. What you need to know before you take GIOTRIF

Do not take GIOTRIF

- if you are allergic to afatinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking this medicine:

- if you are female, have a low body weight of less than 50 kg or have kidney problems. If any of these apply to you, your doctor may monitor you more closely as the side effects may be more pronounced.
- if you have a history of lung inflammation (interstitial lung disease).

- if you have liver problems. Your doctor may do some liver tests. Treatment with this medicine is not recommended if you have a severe liver disease.
- if you have a history of eye problems such as severe dry eyes, inflammation of the transparent layer at the front of the eye (cornea) or ulcers involving the outer part of the eye, or if you use contact lenses.
- if you have a history of heart problems. Your doctor may want to monitor you more closely.

Inform your doctor immediately while taking this medicine:

- if you develop diarrhoea. Treatment at the first signs of diarrhoea is important.
- if you develop skin rash. Early treatment of skin rash is important.
- if you develop new or sudden worsening of shortness of breath, possibly with a cough or fever. These could be symptoms of an inflammation of the lungs (interstitial lung disease) and can be life-threatening.
- if you develop acute or worsening redness and pain in the eye, increased eye watering, blurred vision and/or sensitivity to light. You may need urgent treatment.

See also Possible side effects in section 4.

Children and adolescents

GIOTRIF has not been studied in children or adolescents. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and GIOTRIF

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including herbal medicines and medicines obtained without a prescription.

In particular, if taken before GIOTRIF, the following medicines may increase the blood levels of GIOTRIF and therefore the risk of side effects. They should therefore be taken as far apart in time as possible from GIOTRIF. This means preferably 6 hours (for medicines taken twice daily) or 12 hours (for medicines taken once daily) apart from GIOTRIF:

- Ritonavir, ketoconazole (except in shampoo), itraconazole, erythromycin, nelfinavir, saquinavir - used to treat different kinds of infections.
- Verapamil, quinidine, amiodarone - used to treat heart conditions.
- Cyclosporine A, tacrolimus - medicines that affect your immune system.

The following medicines may reduce the effectiveness of GIOTRIF:

- Carbamazepine, phenytoin, phenobarbital - used to treat seizures.
- St. John's wort (*Hypericum perforatum*), a herbal medicine to treat depression.
- Rifampicin, an antibiotic used to treat tuberculosis.

Ask your doctor if you are unsure of when to take these medicines.

GIOTRIF may increase the blood levels of other medicines including but not limited to:

- Sulfasalazine, used to treat inflammation/infection.
- Rosuvastatin, used for lowering cholesterol.

Tell your doctor before taking these medicines together with GIOTRIF.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

You should avoid becoming pregnant while taking this medicine. If you could become pregnant, you should use adequate birth control methods during treatment and for at least 1 month after taking the last dose of this medicine. This is because there may be a risk that an unborn baby is harmed.

If you become pregnant while receiving this medicine, you should immediately inform your doctor. Your doctor will decide with you whether treatment should be continued or not.

If you plan to become pregnant after taking the last dose of this medicine, you should ask your doctor for advice as your body may not have fully eliminated this medicine.

Breast-feeding

Do not breast-feed while taking this medicine as a risk to the breast-fed child cannot be excluded.

Driving and using machines

If you experience treatment-related symptoms affecting your eye sight (e.g. redness and/or irritation of the eye, dry eye, tearing, light-sensitivity) or your ability to concentrate and react, it is recommended that you do not drive or use machines until the side effect disappears (see section 4 Possible side effects).

GIOTRIF contains lactose

This medicine contains a sugar called lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take GIOTRIF

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage

The recommended dose is 40 mg each day.

Your doctor may adjust (increase or decrease) your dose depending on how well you tolerate this medicine.

When to take GIOTRIF

- It is important to take this medicine without food
- Take this medicine at least 1 hour before eating, or
- If you have already eaten, wait at least 3 hours before taking this medicine.
- Take this medicine once daily about the same time each day. This makes it easier to remember to take this medicine.
- Do not break, chew or crush the tablet.
- Swallow the tablet whole with a glass of still water.

GIOTRIF is to be taken by mouth. If you have difficulties swallowing the tablet, dissolve it in a glass of still water. No other liquids should be used. Drop the tablet into the water without crushing it, and occasionally stir for up to 15 min until the tablet is broken up into very small particles. Drink the liquid straight away. Then fill the glass again with water and drink it to make sure all medicine is taken.

If you are not able to swallow and have a gastric tube your doctor might suggest that the medicine is given to you via the tube.

If you take more GIOTRIF than you should

Contact your doctor or pharmacist immediately. You may experience increased side effects and your doctor may interrupt your treatment and provide supportive care.

If you forget to take GIOTRIF

- If your next scheduled dose is more than 8 hours away, take the missed dose as soon as you remember.
- If your next scheduled dose is due within 8 hours, skip the missed dose and take your next dose at the usual time. Then carry on taking your tablets at regular times as usual.

Do not take a double dose (two tablets instead of one at the same time) to make up for a missed dose.

If you stop taking GIOTRIF

Do not stop taking this medicine without first consulting your doctor. It is important to take this medicine every day, as long as your doctor prescribes it for you. If you do not take this medicine as prescribed by your doctor your cancer may grow again.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, GIOTRIF can cause side effects, although not everybody gets them.

Contact your doctor as soon as possible if you suffer from any of the serious side effects listed below. In some cases your doctor may need to interrupt treatment and reduce your dose or stop treatment:

- **Diarrhoea** (very common, may affect more than 1 in 10 people).
Diarrhoea lasting more than 2 days or more severe diarrhoea may lead to fluid loss (common, may affect up to 1 in 10 people), low blood potassium (common) and worsening kidney function (common). Diarrhoea can be treated. At the first signs of diarrhoea drink plenty of fluids. Contact your doctor immediately and start appropriate antidiarrhoeal treatment as soon as possible. You should have antidiarrhoeal medicine available prior to taking GIOTRIF.
- **Skin rash** (very common).
It is important to treat the rash early. Tell your doctor if a rash starts. If treatment for rash is not working and the rash is getting more severe (for example, you have peeling or blistering of the skin) you should notify your doctor immediately, since your doctor may decide to stop your treatment with GIOTRIF. Rash may occur or worsen in areas exposed to sun. Sun protection with protective clothing and sunscreen is recommended.
- **Inflammation of the lungs** (uncommon, may affect up to 1 in 100 people) called “interstitial lung disease”.
Tell your doctor immediately if you develop new or sudden worsening of shortness of breath, possibly with a cough or fever.
- **Eye irritation or inflammation**
Eye irritation or inflammation may occur (conjunctivitis/keratoconjunctivitis occurs commonly and keratitis uncommonly). Tell your doctor if you have sudden or worsening of eye symptoms such as pain or redness or dry eye.

If you experience any of the symptoms above, contact your doctor as soon as possible.

The following other side effects have also been reported:

Very common side effects (may affect more than 1 in 10 people):

- Mouth sores and inflammation
- Nail infection
- Decreased appetite
- Bleeding from the nose
- Nausea
- Vomiting

Common side effects (may affect up to 1 in 10 people):

- Pain, redness, swelling or peeling of the skin of your hands and feet
- Increased levels of the liver enzymes (aspartate aminotransferase and alanine aminotransferase) in blood tests.

- Inflammation of the lining of the bladder with burning sensations during urination and frequent, urgent need to urinate (cystitis)
- Abnormal taste sensations (dysgeusia)
- Stomach pain, indigestion, heartburn
- Lip inflammation
- Decreased weight
- Runny nose
- Muscle spasms
- Fever

Uncommon side effects (may affect up to 1 in 100 people):

- Inflammation of the pancreas (pancreatitis)

Rare side effects (may affect up to 1 in 1,000 people):

- Severe blistering or peeling of skin (suggestive of Stevens-Johnson syndrome and toxic epidermal necrolysis)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GIOTRIF

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, the pouch and the blister after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture and light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What GIOTRIF contains

- The active substance is afatinib. Each film-coated tablet contains 40 mg of afatinib (as dimaleate).
- The other ingredients are lactose monohydrate, microcrystalline cellulose (E460), colloidal anhydrous silica (E551), crospovidone type A, magnesium stearate (E470b), hypromellose (E464), macrogol 400, titanium dioxide (E171), talc (E553b), polysorbate 80 (E433), indigo carmine (E132) aluminium hydroxide.

What GIOTRIF looks like and contents of the pack

GIOTRIF 40 mg film-coated tablets are light blue and round shaped. They are debossed with the code “T40” on one side and the Boehringer Ingelheim company logo on the other.

GIOTRIF film-coated tablets are available in packs containing 1, 2 or 4 perforated unit dose blisters. Each blister contains 7 x 1 film-coated tablets and is packed together with a desiccant sachet in an aluminium pouch.

Not all pack sizes may be marketed.

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This leaflet was last approved in {MM/YYYY}

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

Package leaflet: Information for the patient

GIOTRIF 50 mg film-coated tablets

afatinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If any of these side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

What is in this leaflet

1. What GIOTRIF is and what it is used for
2. What you need to know before you take GIOTRIF
3. How to take GIOTRIF
4. Possible side effects
5. How to store GIOTRIF
6. Contents of the pack and other information

1. What GIOTRIF is and what it is used for

GIOTRIF is a medicine which contains the active substance afatinib. It works by blocking the activity of a group of proteins called the ErbB family (including EGFR [epidermal growth factor receptor or ErbB1], HER2 [ErbB2], ErbB3 and ErbB4). These proteins are involved in the growth and spread of cancer cells, and can be affected by changes (mutations) in the genes that produce them. By blocking the activity of these proteins this medicine can inhibit growth and spread of cancer cells.

This medicine is used on its own to treat adult patients with a specific type of cancer of the lung (non-small cell lung cancer):

- that is identified by a change (mutation) in the gene for EGFR. GIOTRIF can be prescribed to you as your first treatment or if prior chemotherapy treatment has been insufficient.
- of squamous type if prior chemotherapy treatment has been insufficient.

2. What you need to know before you take GIOTRIF

Do not take GIOTRIF

- if you are allergic to afatinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking this medicine:

- if you are female, have a low body weight of less than 50 kg or have kidney problems. If any of these apply to you, your doctor may monitor you more closely as the side effects may be more pronounced.
- if you have a history of lung inflammation (interstitial lung disease).

- if you have liver problems. Your doctor may do some liver tests. Treatment with this medicine is not recommended if you have a severe liver disease.
- if you have a history of eye problems such as severe dry eyes, inflammation of the transparent layer at the front of the eye (cornea) or ulcers involving the outer part of the eye, or if you use contact lenses.
- if you have a history of heart problems. Your doctor may want to monitor you more closely.

Inform your doctor immediately while taking this medicine:

- if you develop diarrhoea. Treatment at the first signs of diarrhoea is important.
- if you develop skin rash. Early treatment of skin rash is important.
- if you develop new or sudden worsening of shortness of breath, possibly with a cough or fever. These could be symptoms of an inflammation of the lungs (interstitial lung disease) and can be life-threatening.
- if you develop acute or worsening redness and pain in the eye, increased eye watering, blurred vision and/or sensitivity to light. You may need urgent treatment.

See also Possible side effects in section 4.

Children and adolescents

GIOTRIF has not been studied in children or adolescents. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and GIOTRIF

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including herbal medicines and medicines obtained without a prescription.

In particular, if taken before GIOTRIF, the following medicines may increase the blood levels of GIOTRIF and therefore the risk of side effects. They should therefore be taken as far apart in time as possible from GIOTRIF. This means preferably 6 hours (for medicines taken twice daily) or 12 hours (for medicines taken once daily) apart from GIOTRIF:

- Ritonavir, ketoconazole (except in shampoo), itraconazole, erythromycin, nelfinavir, saquinavir - used to treat different kinds of infections.
- Verapamil, quinidine, amiodarone - used to treat heart conditions.
- Cyclosporine A, tacrolimus - medicines that affect your immune system.

The following medicines may reduce the effectiveness of GIOTRIF:

- Carbamazepine, phenytoin, phenobarbital - used to treat seizures.
- St. John's wort (*Hypericum perforatum*), a herbal medicine to treat depression.
- Rifampicin, an antibiotic used to treat tuberculosis.

Ask your doctor if you are unsure of when to take these medicines.

GIOTRIF may increase the blood levels of other medicines including but not limited to:

- Sulfasalazine, used to treat inflammation/infection.
- Rosuvastatin, used for lowering cholesterol.

Tell your doctor before taking these medicines together with GIOTRIF.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

You should avoid becoming pregnant while taking this medicine. If you could become pregnant, you should use adequate birth control methods during treatment and for at least 1 month after taking the last dose of this medicine. This is because there may be a risk that an unborn baby is harmed.

If you become pregnant while receiving this medicine, you should immediately inform your doctor. Your doctor will decide with you whether treatment should be continued or not.

If you plan to become pregnant after taking the last dose of this medicine, you should ask your doctor for advice as your body may not have fully eliminated this medicine.

Breast-feeding

Do not breast-feed while taking this medicine as a risk to the breast-fed child cannot be excluded.

Driving and using machines

If you experience treatment-related symptoms affecting your eye sight (e.g. redness and/or irritation of the eye, dry eye, tearing, light-sensitivity) or your ability to concentrate and react, it is recommended that you do not drive or use machines until the side effect disappears (see section 4 Possible side effects).

GIOTRIF contains lactose

This medicine contains a sugar called lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take GIOTRIF

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage

The recommended dose is 40 mg each day.

Your doctor may adjust (increase or decrease) your dose depending on how well you tolerate this medicine.

When to take GIOTRIF

- It is important to take this medicine without food
- Take this medicine at least 1 hour before eating, or
- If you have already eaten, wait at least 3 hours before taking this medicine.
- Take this medicine once daily about the same time each day. This makes it easier to remember to take this medicine.
- Do not break, chew or crush the tablet.
- Swallow the tablet whole with a glass of still water.

GIOTRIF is to be taken by mouth. If you have difficulties swallowing the tablet, dissolve it in a glass of still water. No other liquids should be used. Drop the tablet into the water without crushing it, and occasionally stir for up to 15 min until the tablet is broken up into very small particles. Drink the liquid straight away. Then fill the glass again with water and drink it to make sure all medicine is taken.

If you are not able to swallow and have a gastric tube your doctor might suggest that the medicine is given to you via the tube.

If you take more GIOTRIF than you should

Contact your doctor or pharmacist immediately. You may experience increased side effects and your doctor may interrupt your treatment and provide supportive care.

If you forget to take GIOTRIF

- If your next scheduled dose is more than 8 hours away, take the missed dose as soon as you remember.
- If your next scheduled dose is due within 8 hours, skip the missed dose and take your next dose at the usual time. Then carry on taking your tablets at regular times as usual.

Do not take a double dose (two tablets instead of one at the same time) to make up for a missed dose.

If you stop taking GIOTRIF

Do not stop taking this medicine without first consulting your doctor. It is important to take this medicine every day, as long as your doctor prescribes it for you. If you do not take this medicine as prescribed by your doctor your cancer may grow again.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, GIOTRIF can cause side effects, although not everybody gets them.

Contact your doctor as soon as possible if you suffer from any of the serious side effects listed below. In some cases your doctor may need to interrupt treatment and reduce your dose or stop treatment:

- **Diarrhoea** (very common, may affect more than 1 in 10 people).
Diarrhoea lasting more than 2 days or more severe diarrhoea may lead to fluid loss (common, may affect up to 1 in 10 people), low blood potassium (common) and worsening kidney function (common). Diarrhoea can be treated. At the first signs of diarrhoea drink plenty of fluids. Contact your doctor immediately and start appropriate antidiarrhoeal treatment as soon as possible. You should have antidiarrhoeal medicine available prior to taking GIOTRIF.
- **Skin rash** (very common).
It is important to treat the rash early. Tell your doctor if a rash starts. If treatment for rash is not working and the rash is getting more severe (for example, you have peeling or blistering of the skin) you should notify your doctor immediately, since your doctor may decide to stop your treatment with GIOTRIF. Rash may occur or worsen in areas exposed to sun. Sun protection with protective clothing and sunscreen is recommended.
- **Inflammation of the lungs** (uncommon, may affect up to 1 in 100 people) called “interstitial lung disease”.
Tell your doctor immediately if you develop new or sudden worsening of shortness of breath, possibly with a cough or fever.
- **Eye irritation or inflammation**
Eye irritation or inflammation may occur (conjunctivitis/keratoconjunctivitis occurs commonly and keratitis uncommonly). Tell your doctor if you have sudden or worsening of eye symptoms such as pain or redness or dry eye.

If you experience any of the symptoms above, contact your doctor as soon as possible.

The following other side effects have also been reported:

Very common side effects (may affect more than 1 in 10 people):

- Mouth sores and inflammation
- Nail infection
- Decreased appetite
- Bleeding from the nose
- Nausea
- Vomiting

Common side effects (may affect up to 1 in 10 people):

- Pain, redness, swelling or peeling of the skin of your hands and feet
- Increased levels of the liver enzymes (aspartate aminotransferase and alanine aminotransferase) in blood tests.

- Inflammation of the lining of the bladder with burning sensations during urination and frequent, urgent need to urinate (cystitis)
- Abnormal taste sensations (dysgeusia)
- Stomach pain, indigestion, heartburn
- Lip inflammation
- Decreased weight
- Runny nose
- Muscle spasms
- Fever

Uncommon side effects (may affect up to 1 in 100 people):

- Inflammation of the pancreas (pancreatitis)

Rare side effects (may affect up to 1 in 1,000 people):

- Severe blistering or peeling of skin (suggestive of Stevens-Johnson syndrome and toxic epidermal necrolysis)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GIOTRIF

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, the pouch and the blister after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture and light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What GIOTRIF contains

- The active substance is afatinib. Each film-coated tablet contains 50 mg of afatinib (as dimaleate).
- The other ingredients are lactose monohydrate, microcrystalline cellulose (E460), colloidal anhydrous silica (E551), crospovidone type A, magnesium stearate (E470b), hypromellose (E464), macrogol 400, titanium dioxide (E171), talc (E553b), polysorbate 80 (E433), indigo carmine (E132) aluminium hydroxide.

What GIOTRIF looks like and contents of the pack

GIOTRIF 50 mg film-coated tablets are dark blue and oval shaped. They are debossed with the code “T50” on one side and the Boehringer Ingelheim company logo on the other.

GIOTRIF film-coated tablets are available in packs containing 1, 2 or 4 perforated unit dose blisters. Each blister contains 7 x 1 film-coated tablets and is packed together with a desiccant sachet in an aluminium pouch.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.