PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

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: contains sugar.
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: contains sugar.
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: contains sugar.
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: contains sugar
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 tablets (tablets).

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 is indicated as monotherapy for the treatment of:

- Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) of adenocarcinoma histology of the lungs (stage IIIB or IV) with Epidermal Growth Factor Receptor mutation(s) Del19 or L858R.
  Efficacy in EGFR-negative tumours has not been established.
- Adult patients with 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 doctor 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.

GIOTRIF should be taken without food. Food should not be consumed for at least 3 hours before and at least 1 hour after taking GIOTRIF (see sections 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 medicines (e.g. loperamide) should be taken immediately and continued for persistent diarrhoea until loose bowel movements cease.
[c] > 48 hours of diarrhoea and/or > 7 days of rash
[d] If patient cannot tolerate 20 mg/day, permanent discontinuation of GIOTRIF should be considered

Interstitial Lung Disease (ILD) should be considered if a patient develops acute or worsening of respiratory symptoms in which case treatment should be interrupted pending evaluation. If ILD is diagnosed, GIOTRIF should be discontinued and appropriate treatment initiated as necessary (see sections 4.3 and 4.4).

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

Use of P-glycoprotein (P-gp) inhibitors
If P-gp inhibitors need to be taken, they should be administered using staggered dosing, i.e. the P-gp inhibitor dose should be taken as far apart in time as possible from the GIOTRIF dose. This means preferably 6 hours (for P-gp inhibitors dosed twice daily) or 12 hours (for P-gp inhibitors dosed once daily) apart from GIOTRIF (see section 4.5).

Special populations
Patients with renal impairment
Exposure to afatinib was found to be increased in patients with moderate or severe renal impairment (see section 5.2). Adjustments to the starting dose are not necessary in patients with mild (eGFR 60 - 89 mL/min/1,73 m²), moderate (eGFR 30 - 59 mL/min/1,73 m²) or severe (eGFR 15 - 29 mL/min/1,73 m²) renal impairment. Monitor patients with severe renal impairment (eGFR 15 - 29 mL/min/1,73 m²) and adjust GIOTRIF dose if not tolerated.
GIOTRIF treatment in patients with eGFR < 15 mL/min/1,73 m² 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 medicine 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 medicine is not recommended.

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

4.3 Contraindications
Hypersensitivity to afatinib or to any of the excipients listed in section 6.1.
Severe (Child Pugh C) hepatic impairment (see section 4.4).
Pregnancy and lactation (see section 4.6).
Ocular/eye conditions/diseases/disorders with severe impairment of vision/eye sight.

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, and fatal outcomes have been reported. 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 medicines especially within the first 6 weeks of the treatment is important and should start at first signs of diarrhoea. Antidiarrhoeal medicines (e.g. loperamide) should be used and if necessary their dose should be escalated to the highest recommended approved dose. Anti-diarrhoeal medicines 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 GIOTRIF (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 sunscreen 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 cases suggestive of Stevens-Johnson syndrome and toxic epidermal necrolysis. Treatment with GIOTRIF 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 $\geq$ 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 GIOTRIF 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 GIOTRIF in less than 1 % of patients. In these patients, confounding factors have included pre-existing liver disease and/or comorbidities associated with progression of underlying malignancy. Periodic liver function testing is recommended in patients with pre-existing liver disease. Dose interruption may become necessary in patients who experience worsening of liver function (see section 4.2). In patients who develop severe hepatic impairment while taking GIOTRIF, treatment should be discontinued.

Gastrointestinal perforations
Gastrointestinal perforation, including fatalities, has been reported during treatment with GIOTRIF in 0,2 % of patients across all randomized controlled clinical trials. In the majority of cases, gastrointestinal perforation was associated with other known risk factors, including concomitant medications such as corticosteroids, NSAIDs, or anti-angiogenic agents, an underlying history of gastrointestinal ulceration, underlying diverticular disease, age, or bowel metastases at sites of perforation. In patients who develop gastrointestinal perforation while taking GIOTRIF, treatment should be

permanently discontinued.

Keratitis
Symptoms such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment should be interrupted or discontinued. GIOTRIF should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration (see section 4.8).

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

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
GIOTRIF contains lactose. Patients with rare hereditary conditions of galactose intolerance (e.g. galactosaemia), total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Interactions with medicine 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, ciclosporin 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, phenobarbitone 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. GIOTRIF may increase the bioavailability of orally administered BCRP substrates (including but not limited to rosuvastatin and sulfasalazine).

Food effect on afatinib
Co-administration of a high-fat meal with GIOTRIF resulted in a significant decrease of exposure to afatinib by about 50 % in regard to C_{max} and 39 % in regard to $AUC_{0-\infty}$. GIOTRIF should be administered without food (see sections 4.2 and 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
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 (see section 4.3).

Pregnancy
GIOTRIF should not be used by women who are pregnant or who are planning to become pregnant.
Mechanistically, all EGFR targeting medicines, such as GIOTRIF, have the potential to cause foetal harm.
If a patient becomes pregnant while or after receiving GIOTRIF, she should be informed of the potential harm to the foetus.

Breastfeeding
Women on treatment with GIOTRIF should not breastfeed their infants. Afatanib is excreted in milk of animals and it is likely that afatinib is excreted in human milk and harm to the baby cannot be excluded.

Fertility
Non-clinical toxicology data have shown effects on reproductive organs at higher doses. Therefore, an adverse effect of GIOTRIF on human fertility cannot be excluded.

4.7 Effects on ability to drive and use machines

Treatment with GIOTRIF may affect the ability to drive and use machines. Patients should not drive and use machines until they know how treatment with GIOTRIF affects them. Ocular adverse reactions (conjunctivitis, dry eye, keratitis) have been reported (see

section 4.8) which may affect the 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 most frequent ADRs were diarrhoea and skin related adverse events (see section 4.4) as well as stomatitis and paronychia. Overall, dose reduction (see section 4.2) led to a lower frequency of common adverse reactions.

Tabulated list of adverse reactions reported during clinical trials

The safety evaluation of GIOTRIF is based on the data from more than 3 800 patients, including more than 1 638 NSCLC patients treated with a daily dose of GIOTRIF 50 mg monotherapy and more than 497 NSCLC patients who received GIOTRIF 40 mg monotherapy once daily.

Adverse Drug Reactions (ADRs) classified by System Organ Class (SOC) and Medical Dictionary for Regulatory Activities (MedDRA) preferred terms reported from any GIOTRIF dosing group per population of all NSCLC trials with daily starting doses of 40 mg and 50 mg GIOTRIF are shown in the Table 2.

Frequency classes: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

Table 2: Side effects identified from all NSCLC trials with daily starting doses of 40 and 50 mg GIOTRIF monotherapy:

System Organ Class (SOC)	MedDRA preferred term	Frequency
Infections and infestations	paronychia[1] cystitis[2]	very common common
Metabolism and nutrition disorders	decreased appetite dehydration hypokalaemia	very common common common
Nervous system disorders	dysgeusia	common
Eye disorders	conjunctivitis dry eye keratitis, photophobia, lacrimation, blurred vision, eye pain	common common uncommon
Respiratory, thoracic and mediastinal disorders	epistaxis[3] rhinorrhoea interstitial lung disease	very common common uncommon
Gastrointestinal disorders	diarrhoea stomatitis[4] nausea vomiting[5] cheilitis[6] dyspepsia pancreatitis gastrointestinal	very common very common very common very common common common uncommon uncommon

System Organ Class (SOC)	MedDRA preferred term	Frequency
	perforation	
Hepatobiliary disorders	increased alanine aminotransferase increased aspartate aminotransferase[7] hepatotoxicity including hepatic failure	common common uncommon
Skin and subcutaneous tissue disorders	rash[8] acneiform dermatitis[9] pruritus[10] dry skin[11,12] nail disorders[13] palmar-plantar erythrodysaesthesia syndrome	very common very common very common very common common common
Musculoskeletal and connective tissue disorders	muscle spasms	common
Renal and urinary disorders	renal impairment/renal failure	common
General disorders and administration site conditions	pyrexia[14]	common
Investigations	decreased weight	common

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

[2] Frequency observed in squamous NSCLC is uncommon

[3] Frequency observed in squamous NSCLC is common

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

[5] Frequency observed in squamous NSCLC is common

[6] Frequency observed in squamous NSCLC is uncommon

[7] Frequency observed in squamous NSCLC is uncommon

[8] Includes group of rash preferred terms

[9] Includes acne, acne pustular, dermatitis acneiform

[10] Includes pruritus, pruritus generalised

[11] Includes dry skin, skin chapped

[12] Frequency observed in squamous NSCLC is common

[13] Includes nail disorder, onycholysis, nail toxicity, onychoclasis, ingrowing nail, nail pitting, onychomadesis, nail discoloration, nail dystrophy, nail ridging, and onychogryphosis

[14] Frequency observed in squamous NSCLC is uncommon

Post-marketing experience
The following adverse reactions have been identified during post-approval use of GIOTRIF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Toxic epidermal necrolysis
- Stevens Johnson syndrome

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms
In overdose side effects can be precipitated and/or be of increased severity. Overdosage has been associated with gastrointestinal events (especially diarrhoea, nausea, vomiting), asthenia, dizziness, headache, abdominal pain and elevated amylase (< 1,5 times ULN). Dermatological events (rash/acne) have also been reported.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 Cytostatic agents

Mechanism of action
Afatinib is a selective, irreversible ErbB Family Blocker. Afatinib covalently binds to and irreversibly blocks signalling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4.

Pharmacodynamic effects
Aberrant ErbB signalling triggered by receptor mutations, and/or amplification, and/or receptor ligand overexpression contributes to the malignant phenotype. Mutation in EGFR defines a distinct molecular subtype of lung cancer.

In non-clinical disease models with ErbB pathway deregulation, afatinib as a single agent effectively blocks ErbB receptor signalling resulting in tumour growth inhibition or tumour regression. NSCLC tumours with common activating EGFR mutations (Del 19, L858R) and several less common EGFR mutations in exon 18 (G719X) and exon 21 (L861Q) are particularly sensitive to afatinib treatment in non-clinical and clinical settings. Limited non-clinical and/or clinical activity was observed in NSCLC tumours with insertion mutations in exon 20.

The acquisition of a secondary T790M mutation is a major mechanism of acquired resistance to afatinib and gene dosage of the T790M-containing allele correlates with the degree of resistance in vitro. The T790M mutation is found in approximately 50 % of patients' tumours upon disease progression on afatinib, for which T790M targeted EGFR TKIs may be considered as a next line treatment option. Other potential mechanisms of resistance to afatinib have been suggested preclinically and MET gene amplification has been observed clinically.

Paediatric population
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/1,73 m², 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/1,73 m², 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/1,73 m²), moderate (eGFR 30 - 59 mL/min/1,73 m²), or severe (eGFR 15 - 29 mL/min/1,73 m²) 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/1,73 m² or on dialysis.

Hepatic impairment
Afatinib is eliminated mainly by biliary/faecal excretion. Subjects with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment had similar exposure in comparison to healthy volunteers following a single dose of 50 mg GIOTRIF. This is consistent with population pharmacokinetic data derived from clinical trials in various tumour types (see "Population pharmacokinetic analysis in special populations" below). No starting dose adjustments appear necessary in patients with mild or moderate hepatic impairment (see section 4.2). The pharmacokinetics of afatinib have not been studied in subjects with severe (Child Pugh C) hepatic dysfunction (see section 4.4).

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

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

Body weight
Plasma exposure ($AUC_{\tau,ss}$) was increased by 26 % for a 42 kg patient ($2,5^{th}$ percentile) and decreased by 22 % for a 95 kg patient ($97,5^{th}$ percentile) relative to a patient weighing 62 kg (median body weight of patients in the overall patient population).

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

Race
Race had no effect on the pharmacokinetics of afatinib based on a population pharmacokinetic analysis, including patients of Asian, White, and Black racial groups. Data on Black racial groups was limited.

Renal impairment
Exposure to afatinib moderately increased with lowering of the creatinine clearance (CrCL, calculated according to Cockcroft Gault), i.e. for a patient with a CrCL of 60 mL/min or 30 mL/min exposure ($AUC_{\tau,ss}$) to afatinib increased by 13 % and 42 %,

respectively, and decreased by 6 % and 20 % for a patient with CrCL of 90 mL/min or 120 mL/min, respectively, compared to a patient with the CrCL of 79 mL/min (median CrCL of patients in the overall patient population analysed).

Hepatic impairment
Patients with mild and moderate hepatic impairment as identified by abnormal liver tests did not correlate with any significant change in afatinib exposure. There was limited data available for moderate and severe hepatic impairment.

Other patient characteristics/intrinsic factors
Other patient characteristics/intrinsic factors found with a significant impact on afatinib exposure were: ECOG performance score, lactate dehydrogenase levels, alkaline phosphatase levels and total protein. The individual effect sizes of these covariates were considered not clinically relevant. Smoking history, alcohol consumption (limited data), or presence of liver metastases had no significant impact on the pharmacokinetics of afatinib.

Other information on medicine interactions
Interactions with medicine uptake transport systems
In vitro data indicated that 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, GIOTRIF 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 interactions with afatinib due to inhibition of UGT1A1 are considered unlikely.

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 aluminium hydroxide (E132)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store at or below 30 °C.
Store in the original package in order to protect from moisture and light.
KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container
GIOTRIF film-coated tablets are packed in blister strips, consisting of a PVC/PVDC forming sheet and a printed aluminium lidding foil.
Each blister strip of 7 tablets is pouched in a laminated aluminium foil pouch with a dessicant sachet; 4 blister strips are packed per printed cardboard carton, in packs of 28 tablets.

6.6 Special precautions for disposal
No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Ingelheim Pharmaceuticals (Pty) Ltd
Suite 1, Building 4, 2nd Floor
Waterfall Corporate Campus
74 Waterfall Drive
Midrand
South Africa

8. REGISTRATION NUMBERS
GIOTRIF 20 mg: 47/26/1016
GIOTRIF 30 mg: 47/26/1017
GIOTRIF 40 mg: 47/26/1018
GIOTRIF 50 mg: 47/26/1019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 19 May 2020

10. DATE OF REVISION OF THE TEXT

22 August 2024