SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Afatinib 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Afatinib 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). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet). Afatinib 40 mg film-coated tablets A yellow colored ellipse shaped shallow biconvex film coated tablet having plain on both side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Afatinib 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);

• 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 Afatinib 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 Afatinib 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). Afatinib treatment should be continued until disease progression or until no longer tolerated by the patient (see Table 1 below). Dose adjustment for adverse reactions

Symptomatic adverse 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 Afatinib as outlined in Table 1 (see sections 4.4 and 4.8). Table 1: Dose adjustment information for adverse reactions CTCAEa Adverse reactions Recommended dosing Grade 1 or Grade 2 No interruption b No dose adjustment Grade 2 (prolonged c or intolerable) or Interrupt until Grade 0/1 b Resume with dose reduction by 10 mg decrements d Grade ≥ 3 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 Afatinib 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, Afatinib 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 Afatinib 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 Afatinib (see section 4.5). Special populations Patients with renal impairment Exposure to afatinib was found to be increased in patients with moderate or severe renal impairment (see section 5.2). Adjustments to the starting dose are not necessary in patients with mild (eGFR 60-89 mL/min/1.73m²), moderate (eGFR 30-59 mL/min/1.73m²) or severe (eGFR 15-29 mL/min/1.73m²) renal

impairment. Monitor patients with severe renal impairment (eGFR 15-29 mL/min/1.73m²) and adjust

GIOTRIF dose if not tolerated. GIOTRIF treatment in patients with eGFR <15 mL/min/1.73m² or on dialysis is not recommended. Patients with hepatic

impairment Exposure to afatinib is not significantly changed in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment (see section 5.2). Adjustments to the starting dose are not necessary in patients with mild or moderate hepatic impairment. This medicinal product has not been studied in patients with severe (Child Pugh C) hepatic impairment. Treatment in this population is not recommended (see section 4.4). Pediatric 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 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.

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. Diarrhea 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, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with drug transport systems Effects of P-gp and breast cancer resistance protein (BCRP) inhibitors on afatinib In vitro studies have demonstrated that afatinib is a substrate of P-gp and BCRP. When the strong P-gp and BCRP inhibitor ritonavir (200 mg twice a day for 3 days) was administered 1 hour before a single dose of 20 mg GIOTRIF, exposure to afatinib increased by 48% (area under the curve (AUC0-∞)) and 39% (maximum plasma concentration (Cmax)). In contrast, when ritonavir was administered simultaneously or 6 hours after 40 mg GIOTRIF, the relative bioavailability of afatinib was 119% (AUC0-∞) and 104%

(Cmax) and 111% (AUC0-∞) and 105% (Cmax), 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% (AUC0-∞) and 22% (Cmax) 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 Cmax and 39% in regard to AUC0-∞. 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 summaries the frequencies of ADRs from all NSCLC trials and from post-marketing experience with daily GIOTRIF doses of 40 mg or 50 mg as monotherapy. The following terms are used to rank the ADRs by frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in

order of decreasing seriousness. Table 2: Summary of ADRs per frequency category Body System Very common Common Uncommon Rare Infections and infestations Paronychia1 Cystitis Metabolism and nutrition Decreased Dehydration disorders appetite Hypokalaemia Nervous system disorders Dysgeusia Eye disorders Conjunctivitis Keratitis Dry eye Respiratory, thoracic and Epistaxis Rhinorrhoea Interstitial lung mediastinal disorders disease Gastrointestinal disorders Diarrhoea Dyspepsia Pancreatitis Stomatitis2 Cheilitis Nausea Vomiting Hepatobiliary disorders Alanine aminotransferase increased Aspartate aminotransferase increased Skin and subcutaneous tissue Rash3 Palmar-plantar Stevens-Johnson disorders erythrodysaesthesia syndrome7 Dermatitis syndrome acneiform4 Toxic epidermal Nail disorders8 necrolysis7 Pruritus5 Dry skin6 Musculoskeletal and Muscle spasms connective tissue disorders Renal and urinary disorders Renal impairment/ Renal failure General disorders and Pyrexia administration site conditions Investigations Weight decreased

1 Includes Paronychia, Nail infection, Nail bed infection

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

erosion, Mucosal erosion, Mucosal ulceration

3 Includes group of rash preferred terms

4 Includes Acne, Acne pustular, Dermatitis acneiform

5 Includes Pruritus, Pruritus generalised

6 Includes Dry skin, Skin chapped

7 Based on post-marketing experience

8 Includes Nail disorder, Onycholysis, Nail toxicity, Onychoclasis, Ingrowing nail, Nail pitting,

Onychomadesis, Nail discoloration, Nail dystrophy, Nail ridging, and Onychogryphosis Description of selected adverse reactions Very common ADRs in GIOTRIF-treated patients occurring in at least 10% of patients in trial LUX-Lung 3 and LUX-Lung 7 are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Tables 3 and 4. Table 3: Very common ADRs in trial

LUX-Lung 3 GIOTRIF Pemetrexed/ (40 mg/day) Cisplatin N=229 N=111 NCI-CTC Grade Any Grade 3 4 Any Grade 3 4 MedDRA Preferred Term % % % % % % Infections and infestations Paronychia1 57.6 11.4 0 0 0 0 Metabolism and nutrition disorders Decreased appetite 20.5 3.1 0 53.2 2.7 0 Respiratory, thoracic and mediastinal disorders Epistaxis 13.1 0 0 0.9 0.9 0 Gastrointestinal disorders Diarrhoea 95.2 14.4 0 15.3 0 0 Stomatitis2 69.9 8.3 0.4 13.5 0.9 0 Cheilitis 12.2 0 0 0.9 0 0 Skin and subcutaneous tissue disorders Rash3 70.3 14 0 6.3 0 0 Dermatitis acneiform4 34.9 2.6 0 0 0 0 Dry skin5 29.7 0.4 0 1.8 0 0 Pruritus6 19.2 0.4 0 0.9 0 0 Investigations Weight decreased 10.5 0 0 9.0 0 0

1 Includes Paronychia, Nail infection, Nail bed infection

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

Mucosal erosion, Mucosal ulceration

3 Includes group of rash preferred terms

4 Includes Acne, Acne pustular, Dermatitis acneiform

5 Includes Dry skin, Skin chapped

6 Includes Pruritus, Pruritus generalized

Table 4: Very common ADRs in trial LUX-Lung 7 GIOTRIF Gefitinib (40 mg/day) N=160 N=159 NCI-CTC Grade Any 3 4 Any 3 4 Grade Grade MedDRA Preferred Term % % % % % % Infections and infestations Paronychia1 57.5 1.9 0 17.0 0.6 0 Cystitis2 11.3 1.3 0 7.5 1.3 0.6 Metabolism and nutrition disorders Decreased appetite 27.5 1.3 0 24.5 1.9 0 Hypokalaemia3 10.6 2.5 1.3 5.7 1.3 0 Respiratory, thoracic and mediastinal disorders Rhinorrhoea4 19.4 0 0 7.5 0 0 Epistaxis 18.1 0 0 8.8 0 0 Gastrointestinal disorders Diarrhoea 90.6 13.8 0.6 64.2 3.1 0 Stomatitis5 64.4 4.4 0 27.0 0 0 Nausea 25.6 1.3 0 27.7 1.3 0 Vomiting 19.4 0.6 0 13.8 2.5 0 Dyspepsia 10.0 0 0 8.2 0 0 Hepatobiliary disorders Alanine aminotransferase increased 11.3 0 0 27.7 8.8 0.6 Skin and subcutaneous tissue disorders Rash6 80.0 7.5 0 67.9 3.1 0 Dry skin 32.5 0 0 39.6 0 0 Pruritus7 25.6 0 0 25.2 0 0 Dermatitis acneiform8 23.8 1.9 0 32.1 0.6 0 General disorders and administration site

conditions Pyrexia 13.8 0 0 6.3 0 0 Investigations Weight decreased 10.0 0.6 0 5.7 0.6 0

1 Includes Paronychia, Nail infection, Nail bed infection

2 Includes Cystitis, Urinary tract infection

3 Includes Hypokalaemia, Blood potassium decreased

4 Includes Rhinorrhoea, Nasal inflammation

5 Includes Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Mucosal erosion

6 Includes group of rash preferred terms

7 Includes Pruritus, Pruritus generalised

8 Includes Dermatitis acneiform, Acne

Liver function test abnormalities Liver function test abnormalities (including elevated ALT and AST) were observed in patients receiving GIOTRIF 40 mg. These elevations were mainly transient and did not lead to discontinuation. Grade 2 (>

2.5 to 5.0 times upper limit of normal (ULN)) ALT elevations occurred in < 8% of patients treated with this

medicinal product. Grade 3 (> 5.0 to 20.0 times ULN) elevations occurred in <4% of patients treated with GIOTRIF (see section 4.4). Description of selected adverse reactions Very common ADRs in GIOTRIF-treated patients occurring in at least 10% of patients in trial LUX-Lung 8 are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 5. Table 5: Very common ADRs in trial LUX-Lung 8* GIOTRIF Erlotinib (40 mg/day) N=395 N=392 NCI-CTC Grade Any Grade 3 4 Any Grade 3 4 MedDRA Preferred Term % % % % % % Infections and infestations Paronychia1 11.0 0.5 0 5.1 0.3 0 Metabolism and nutrition disorders Decreased appetite 24.7 3.1 0 26.1 2.0 0 Gastrointestinal disorders Diarrhoea 74.7 9.9 0.8 41.3 3.0 0.3 Stomatitis2 30.1 4.1 0 10.6 0.5 0 Nausea 20.7 1.5 0 16.2 1.0 0.3 Skin and subcutaneous tissue disorders Rash3 60.7 5.4 0 56.7 8.1 0 Dermatitis acneiform4 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).

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. 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.

5.2 Pharmacokinetic properties

Absorption Following oral administration of GIOTRIF, Cmax of afatinib were observed approximately 2 to 5 hours post

dose. Cmax and AUC0-∞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% (Cmax) and 39% (AUC0-∞), 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,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 (AUC0-∞) and 2.11-fold (Cmax). 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% (Cmax) and 122% (AUC0-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% (Cmax) and 150% (AUC0-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,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,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,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 CYP3A4dependent 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

Pregelatinised Starch BP Copovidone BP Sodium Starch Glycolate BP Croscarmellose Sodium BP Magnesium Stearate BP Colloidal Anhydrous Sillica BP Purified talc BP Ludipress Ph. Grade

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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 aluminum pouch and contains 10 film-coated tablets. Pack sizes of 3 X 10's..

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Beacon Medicare Limited 9/B/2 Toyenbee Circular Road Motijheel, Dhaka Bangladesh.

8. MARKETING AUTHORISATION NUMBER(S)

H2022/CTD8862/20125

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2022 April 10

10. DATE OF REVISION OF THE TEXT

2022 April 10