AFATIN 20 (Afatinib Film Coated Tablets 20mg)
AFATIN 30 (Afatinib Film Coated Tablets 30mg)
AFATIN 40 (Afatinib Film Coated Tablets 40mg)
2xxxxxx

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AFATIN 40 (Afatinib Film Coated Tablets 40mg)

NAME OF ACTIVE INGREDIENT
AFATIN 20: Each film-coated tablet contains 20 mg afatinib (as dimaleate).
AFATIN 30: Each film-coated tablet contains 30 mg afatinib (as dimaleate).
AFATIN 40: Each film-coated tablet contains 40 mg afatinib (as dimaleate).

DOSAGE FORM
Film-coated tablet

PRODUCT DESCRIPTION
Afatinib Film Coated Tablets 20mg:
White to off white, round biconvex, bevel-edged, film coated tablets debossed with 'A2' on one side and 'H' on other side and free from physical defects. Diameter : Approximately 7.90 mm

Afatinib Film Coated tablets 30mg:
White to off white, round biconvex, bevel edge film coated tablets debossed with 'A3' on one side and 'H' on other side and free from physical defects. Diameter : Approximately 8.90 mm

Afatinib Film Coated Tablets 40mg:
White to off-white, round biconvex, bevel-edged, film coated tablets, debossed with 'A4' on one side and 'H' on the other side. Diameter : Approximately 9.90 mm

PHARMACODYNAMICS
Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EB03.

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

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

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

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

PHARMACOKINETICS
Absorption
Following oral administration of afatinib, C_{max} of afatinib were observed approximately 2 to 5 hours post dose. C_{max} and AUC0-∞ values increased slightly more than proportionally in the dose range from 20 mg to 50 mg afatinib. Systemic exposure to afatinib is decreased by 50% (C_{max}) 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 ($AUC_{T,ss}$) was observed when food was consumed within 3 hours before or 1 hour after taking afatinib. Therefore, food should not be consumed for at least 3 hours before and at least 1 hour after taking afatinib.

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 (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. 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. Afatinib 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. No starting dose adjustments appear necessary in patients with mild or moderate hepatic impairment. The pharmacokinetics of afatinib have not been studied in subjects with severe (Child Pugh C) hepatic dysfunction.

Population pharmacokinetic analysis in special populations
No starting dose adjustment was considered necessary for any of the following covariates.

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

Body weight
Plasma exposure ($AUC_{T,ss}$) 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 ($AUC_{T,ss}$), 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 ($AUC_{T,ss}$) to afatinib increased by 13% and 42%, respectively, and decreased by 6% and 20% for a patient with CrCL of 90 mL/min or 120 mL/min, respectively, compared to a patient with the CrCL of 79 mL/min (median CrCL of patients in the overall patient population analysed).

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

Other patient characteristics/intrinsic factors
Other patient characteristics/intrinsic factors found with a significant impact on afatinib exposure were:

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

Paediatric population
After administration of 18 mg/m2 afatinib, the steady-state exposure (AUC and Cmax) in paediatric patients
aged 2 to less than 18 years was comparable to that observed in adults given 40-50 mg 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 OATP1B1, 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 FM03 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.

INDICATIONS
AFATIN 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.

RECOMMENDED DOSE
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.

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. Afatinib 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 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 afatinib as outlined in Table 1.

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 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.

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.

Special populations
Patients with renal impairment
Exposure to afatinib was found to be increased in patients with moderate or severe renal impairment. Adjustments to the starting dose are not necessary in patients with mild (eGFR 60-89 mL/min/1.73m^2), moderate (eGFR 30-59 mL/min/1.73m^2) or severe (eGFR 15-29 mL/min/1.73m^2) renal impairment. Monitor patients with severe renal impairment (eGFR 15-29 mL/min/1.73m^2) and adjust afatinib dose if not tolerated.

Afatinib treatment in patients with eGFR < 15 mL/min/1.73m^2 or on dialysis is not recommended.

Patients with hepatic impairment
Exposure to afatinib is not significantly changed in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. 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.

Paediatric population
There is no relevant use of afatinib in the paediatric population in the indication of NSCLC.

Treatment of children or adolescents with afatinib was not supported by a clinical trial conducted in paediatric patients and with other conditions. Safety and efficacy have not been established.

Therefore, treatment of children or adolescents with this medicinal product is not recommended.

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

ROUTE OF ADMINISTRATION
Oral

CONTRAINDICATIONS
Hypersensitivity to afatinib or to any of the excipients.

WARNINGS AND PRECAUTIONS
Assessment of EGFR mutation status
When assessing the EGFR mutation status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

Diarrhoea
Diarrhoea, including severe diarrhoea, has been reported during treatment with afatinib. 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. Anti-diarrhoeal 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 afatinib. 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. 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 afatinib treatment. Patients with severe skin reactions may also require temporary interruption of therapy, dose reduction, 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.

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. 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 afatinib for treatment of NSCLC. ILD-like adverse reactions were reported in 0.7% of patients treated with AFATINIB 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, afatinib should be permanently discontinued and appropriate treatment initiated as necessary.

Severe hepatic impairment

Dimensions: 300 X 400mm
BLACK

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. Dose interruption may become necessary in patients who experience worsening of liver function. In patients who develop severe hepatic impairment while taking afatinib, treatment should be discontinued.

Gastrointestinal perforations
Gastrointestinal perforation, including fatalities, has been reported during treatment with afatinib 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 afatinib, treatment should be permanently discontinued.

Keratitis
Symptoms such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. This medicinal product should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.

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.

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.

INTERACTIONS WITH OTHER MEDICAMENTS

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 afatinib, exposure to afatinib increased by 48% (area under the curve (AUC0-∞)) and 39% (maximum plasma concentration (C_{max})). In contrast, when ritonavir was administered simultaneously or 6 hours after 40 mg afatinib, the relative bioavailability of afatinib was 119% (AUC0-∞) and 104% (C_{max}) and 111% (AUC0-∞) 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 afatinib.

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% (C_{max}) after administration of a single dose of 40 mg afatinib. 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.

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 afatinib 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 afatinib resulted in a significant decrease of exposure to afatinib by about 50% in regard to C_{max} and 39% in regard to AUC0-∞. Thismedicinal product should be administered without food.

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 afatinib. 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. 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.

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 afatinib, 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. 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.

SIDE EFFECTS

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

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

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

[3] Includes group of rash preferred terms

[4] Includes Acne, Acne pustular, Dermatitis acneiform

[5] Includes Pruritus, Pruritus generalised

[6] Includes Dry skin, Skin chapped

[7] Based on post-marketing experience

[8] Includes Nail disorder, Onycholysis, Nail toxicity, Onychoclasis, Ingrowing nail, Nail pitting, Onychomadesis, Nail discoloration, Nail dystrophy, Nail ridging, and Onychogryphosis

SYMPTOMS AND TREATMENT OF 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, afatinib should be withheld and supportive care instituted. If indicated, elimination of unabsorbed afatinib may be achieved by emesis or gastric lavage.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Afatinib 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 which may affect patients ability to drive or use machines.

PHARMACEUTICAL PARTICULARS

List of excipients:
Tablet core: Lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate.

Film-coating (Opadry): Hypromellose (E464), Titanium dioxide (E171), Talc (E553b), Macrogol (E1521), Polysorbate 80 (E433).

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

Dosage form and packaging available:
3 x 10's Dessicant Alu-Alu Blister Pack
Each blister is packed together with a silica gel sachet 4gm (2gm sg + 2gm ms) in a triple laminated pouch (12 micron PET/ 12 micron aluminium/ 75micron LDPE).
3 pouches in a plain carton with a leaflet.

Product Registration Holder:
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