PVI.Table 3 (cont'd) Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important missing information		
Paediatric patients (<18 years)	Routine risk minimisation by routine pharmacovigilance and appropriate labelling in the SmPC (Section 4.2).	None
Patients with severe renal impairment	Routine risk minimisation by routine pharmacovigilance and appropriate labelling in the SmPC (Sections 4.2 and 5.2).	None
Patients with severe hepatic impairment	Routine risk minimisation by routine pharmacovigilance and appropriate labelling in the SmPC (Sections 4.2 and 5.2).	None
Patients with cardiac impairment	Routine risk minimisation by routine pharmacovigilance and appropriate labelling in the SmPC (Section 4.4).	None
Chemotherapy pre-treated patients with EGFR M +NSCLC (additional characterisation)	Routine risk minimisation by routine pharmacovigilance	None

PART VI.2 ELEMENTS FOR A PUBLIC SUMMARY

Part VI.2.1 Overview of disease epidemiology

Non-small cell lung cancer (NSCLC) accounts for most lung cancers worldwide. Studies have found that NSCLC rates ranged from 26.6 to 93.0 cases per 100 000 men and from 6.1 to 33.1 cases per 100 000 women. A genetic factor known as an epidermal growth factor receptor (EGFR) mutation is important in planning medications for NSCLC. Afatinib is intended to treat patients with advanced NSCLC with an EGFR mutation.

Patients with advanced NSCLC have a poor prognosis, with median survival times of only 8 to 11 months in randomised clinical trials of platinum-based chemotherapy. Recent trials of EGFR tyrosine kinase inhibitors (TKIs) drugs have reported longer median survival especially in patients with EGFR mutations.

Risk factors for NSCLC include use of tobacco, advanced age, male sex, personal history of lung disease, some occupational or environmental exposures, air pollution, and family history. Risk factors for NSCLC that has the EGFR mutation include female gender, non smokers and Asian ethnicity.

Part VI.2.2 Summary of treatment benefits

The prognosis for advanced disease remains poor, with an overall 5-year survival rate of 9% to 13%.While chemotherapy has demonstrated modest effects in NSCLC, targeted therapies for lung cancers with certain cell markers have emerged as a new method to treat specific types of lung cancer.

One type of cell marker is called the EGFRs. These are also known as human epidermal growth factor receptors (HERs) or ErbB receptors, and are a family of receptors called EGFR (ErbB1), HER2 (ErbB2), ErbB3, and ErB4. In the recent years, EGFR TKIs have been introduced as targeted therapy for the treatment of patients with NSCLC. Afatinib is a potent and selective, irreversible ErbB family blocker.

Afatinib provides clinically meaningful benefit in the treatment of patients with advanced or metastatic NSCLC whose tumours have mutations of the EGFR, by delaying the time to disease progression and providing control of disease-related symptoms. A consistent treatment benefit of afatinib has been demonstrated in EGFR TKI-naïve patients with EGFR mutation positive NSCLC.

Part VI.2.3 Unknowns relating to treatment benefits

In clinical trials, afatinib exerted a consistent treatment benefit across other patient subpopulations defined by age, gender, race, geographical region, smoking status, and Eastern Cooperative Oncology Group (ECOG) performance status.

Experience is limited in patients with severe renal or hepatic impairment and patients with cardiac impairment. There is no evidence to suggest that efficacy would be any different in these patients.

Part VI.2.4 Summary of safety concerns

PVI.Table 4 Important identified risks

Risk	What is known	Preventability
Diarrhoea (incl. excessive loss of body water [dehydration] and renal impairment secondary to diarrhoea)	Diarrhoea is a common side effect of treatment with afatinib and other drugs belonging to the class of the EGFR TKI. Diarrhoea occurs in nearly all treated patients (in 8-9 patients out of 10), usually starting within 2 weeks of exposure to afatinib. Diarrhoea is mostly of mild to moderate intensity, and 7 in 10 patients recover without any consequences. Approximately 1 out of 5 patients will need to reduce afatinib dose, but less than 4 patients out of 100 will need to stop the treatment with afatinib, because of diarrhoea. Since diarrhoea causes gastrointestinal fluid loss, excessive loss of body water (dehydration) may occur. This is an uncommon event, which develops in 3-5 patients out of 100. A further side effect, which may be caused by diarrhoea and dehydration, is abnormal renal function, which occurs in 3-4 patients out of 100. Both dehydration and renal impairment are in most cases of mild intensity (grade 1 and 2) and resolve after treatment without consequences. Severe diarrhoea can develop at increased risk in female patients, in patients of low body weight (below 50 kg), and in those who already have low renal function.	At first signs of diarrhoea, proactive management should start. This includes adequate administration of intravenous fluids and of anti-diarrhoeal drugs, especially in the first 6 weeks of afatinib treatment. Patients with severe diarrhoea may require interruption or dose adjustment of therapy with afatinib. Patients who become dehydrated may require administration of intravenous electrolytes and fluids. This proactive management, together with afatinib dose interruption or reduction when necessary, leads to improvement of diarrhoea and to lower occurrence of dehydration and renal impairment. Female patients, those of low body weight, and those with impaired renal function, should be kept under close monitoring. This is described under “special warnings and precautions for use” in section 4.4 of the SmPC.

PVI.Table 4 (cont'd) Important identified risks

Risk	What is known	Preventability
Severe skin reactions	Severe skin reactions were identified by using the term "rash/acne", which is used in the following to describe the known data. Rash/acne is a common side effect of treatment with afatinib and other drugs belonging to the EGFR TKI class. Rash/acne occurs in 7-9 patients out of 10, usually starting within 4 weeks of exposure to afatinib. Rash/acne is mostly of mild to moderate intensity. Severe skin reactions are rarely seen. Less than 20 patients out of 100 will need to reduce afatinib dose, but less than 2 patients out of 100 will need to stop the treatment with afatinib, because of rash/acne. Rarely, severe forms of skin reactions such as bullous, blistering and exfoliative skin conditions have been reported during afatinib treatment, including very rare cases suggestive of Stevens-Johnson syndrome (in 2 patients out of 3865). Rash/acne occurs more frequently at higher afatinib doses. Patients with abnormal renal function, those of low body weight (below 50 kg), and female patients, are at increased risk to develop rash/acne.	To improve afatinib tolerability, patients should be closely monitored. Proactive therapeutic management includes for example early administration of emollients or antibiotics. For patients who are exposed to sun, protective clothing and/or use of sun screen is advisable. In case of prolonged or severe skin reactions, it may be necessary to reduce or interrupt afatinib treatment and to administer additional dermatological therapy. If the patient develops severe bullous, blistering or exfoliating skin conditions, afatinib treatment should be interrupted or discontinued. Patients of low body weight, those with impaired renal function, and female patients, should be kept under close monitoring. This is described under "special warnings and precautions for use" in section 4.4 of the SmPC.

PVI.Table 4 (cont'd) Important identified risks

Risk	What is known	Preventability
ILD	Interstitial lung disease is a potentially fatal side effect of drugs belonging to the EGFR TKI class. Interstitial lung disease includes several lung diseases affecting the tissue and space around the air sacs of the lungs (interstitium). In mild cases, it can be asymptomatic and only present with mild abnormal Xray findings. In more severe cases, it may cause shortness of breath (dyspnoea) and lead to a serious inflammatory reaction of the lung tissue (acute respiratory distress syndrome), which can be life-threatening or fatal. Upon afatinib treatment, interstitial lung disease (ILD) occurs at low frequency, in 1.5% of patients, 1 event in 3864 patients was fatal. Slightly more than half of patients who had ILD due to afatinib treatment were of Asian ethnicity. Risks for ILD are a combination of chemotherapeutic drugs, with or without radiotherapy, and pre-existing ILD. Interstitial lung disease may develop at increased risk in patients who smoke.	Interstitial lung disease should be carefully investigated and excluded in patients with acute or worsening pulmonary symptoms (including shortness of breath, cough, and fever). Treatment with afatinib should be interrupted during pending investigation of these symptoms. If ILD is diagnosed, afatinib should be permanently discontinued and appropriate treatment administered as necessary. This is described under “special warnings and precautions for use” in section 4.4 of the SmPC.
Keratitis	Keratitis is an inflammation of the transparent front part of the eye (cornea) and is a side effect known in EGFR TKI class. Upon afatinib treatment, keratitis occurs rarely (in 1 out of 1000 patients) and is mostly of mild intensity. Keratitis may occur especially in patients who already have eye problems due to EGFR TKI treatment.	Patients with acute or worsening symptoms such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye, should be referred promptly to an ophthalmology specialist. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Afatinib should be used with caution in patients who previously had keratitis, ulcerative keratitis, or severe dry eye. Contact lens use also increases the possibility of keratitis and ulceration. This is described under “special warnings and precautions for use” in section 4.4 of the SmPC.

PVI.Table 4 (cont'd) Important identified risks

Risk	What is known	Preventability
Hepatic impairment	Liver impairment is a risk in all drugs in the EGFR TKI class. Liver failure, including fatalities, has been reported during treatment with afatinib in less than 1 patient out of 100. In these patients, other contributing factors were present, such as pre-existing liver disease and/or other diseases associated with progression of lung cancer. Compared to patients with normal liver function at start of treatment, patients who had impaired hepatic function before starting afatinib treatment were more likely to experience an elevation of liver enzymes (alanine aminotransferase and/or aspartate aminotransferase) or hepatic impairment.	Hepatic failure, including fatalities, has been reported during treatment with afatinib in less than 1% of patients. In these patients, confounding factors have included pre-existing liver disease and/or co-morbidities associated with progression of underlying malignancy. Periodic liver function testing is recommended in patients with pre-existing liver disease. Afatinib 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. This is described under “special warnings and precautions for use” in section 4.4 of the SmPC.

PVI.Table 5 Important potential risks

Risk	What is known (incl. reason why it is considered a potential risk)
Decreased blood fraction pumped by the left ventricle [decreased LVEF]/heart failure	Decreased left ventricular ejection fraction (LVEF) or heart failure occurred rarely (in less than 2 patients out of 100) upon afatinib treatment; moreover, in some cases they might have been caused by cardiac toxicity of other chemotherapic drugs. There was no indication that afatinib might be associated with heart failure. Only in very few patients (slightly more than 1 in 100), the decrease of LVEF was clinically significant. Where follow-up information was available, there was a tendency for such changes to recover although afatinib treatment was not interrupted.

PVI.Table 5 (cont'd) Important potential risks

Risk	What is known (incl. reason why it is considered a potential risk)
Pancreatitis	In clinical trials with afatinib, pancreatitis occurred in less than 1 out of 100 patients. In several cases, pancreatitis developed up to 8 days after discontinuation of afatinib. All patients, except 1 who experienced pancreatitis due to cancer progression, fully recovered. For all cases with sufficient documentation there were alternative explanations for pancreatitis occurrence: biliary disease, possible infectious or ischemic causes, cancer progression, and/or concomitant medications associated with pancreatitis. No specific risk factors for pancreatitis were identified.
Developmental toxicity	Although there were no serious findings in the developmental toxicity studies, there is a concern for adverse effects on embryo-foetal development based on the mechanism of action of afatinib. Therefore, developmental toxicity was added as an important potential risk.
Gastrointestinal perforation	Gastrointestinal perforation is a side effect for other medicinal products of the same therapeutic class (EGFR inhibitors) as afatinib (class effect). Therefore, there is a certain probability that the event may also be caused by afatinib. However, gastrointestinal perforation occurred in about 1 of 1000 patients with none of the cases being assessed as drug-related by the investigator or Boehringer Ingelheim. Risk factors for gastrointestinal perforation include concomitant medications such as steroids or non-steroidal anti-inflammatory drugs, underlying history of gastrointestinal ulceration, age, smoking or bowel metastases at sites of perforation.
Hypersensitivity reactions	Based on how afatinib is carried in the blood, there is a small chance of an allergic reaction to afatinib. In clinical trials hypersensitivity (allergic) reactions occurred in about 2 of 1000 patients. From 9 cases reported overall, 2 were assessed as drug-related, which were both non-serious and of mild severity (grade 1 or 2). Risk groups or risk factors are unknown.

PVI.Table 6 Important missing information

Risk	What is known
Lack of information on use in paediatric patients (<18 years)	Paediatric patients (younger than 18 years) were excluded from participation in clinical studies with afatinib; therefore, there is no safety information on use of afatinib in children and adolescents. Treatment of children and adolescents with afatinib is currently not recommended. However, there is no relevant use of afatinib in the paediatric population in the indication of NSCLC, which is usually diagnosed in patients older than 70 years.
Limited information on use in patients with severe renal impairment	Renal side effects observed in clinical studies were reversible and mostly due to renal effects secondary to diarrhoea and dehydration. In addition, no increase of risks for afatinib use in patients with mild and moderate renal impairment is expected and no dose adjustment is needed. However, due to the lack of data on patients with severe renal impairment, afatinib use in these patients is not recommended.
Limited information on use in patients with severe hepatic impairment	Afatinib is not metabolised by the liver. No increased risks are expected for afatinib use in patients with mild and moderate liver impairment and no dose adjustment is needed. Periodic liver function testing is recommended in patients with pre-existing mild and moderate hepatic impairment. However, since there are no studies on patients with severe liver impairment, and in view of the potential risk of liver failure, afatinib use is not recommended in these patients.
Limited information on use in patients with cardiac impairment	In non-clinical and clinical studies, afatinib showed no potential for cardiac effects. However, in view of the potential risk of decreased LVEF/heart failure common to the EGFR TKI class, careful use of afatinib and possibly cardiac monitoring are recommended in patients with pre-existing cardiac impairment.
Chemotherapy pre-treated patients with EGFR M +NSCLC (additional characterisation)	Available clinical data in chemotherapy pre-treated patients does not show any safety concerns for this population. However, as the information is limited at the current point in time, a study is performed for further characterisation of safety.

Part VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The SmPC and the PL for Giotrif can be found in Giotrif's EPAR page. This medicine has no additional risk minimisation measures.

Part VI.2.6 Planned post-authorisation development plan

PVI.Table 7 List of studies in the post-authorisation development plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Pharmacokinetics of afatinib for the determination of washout following multiple and prolonged dosing (cat 3)	Time for complete wash out of afatinib	Developmental toxicity	Planned	Q4 2015 (planned)
Additional safety and efficacy data of afatinib 40mg qd in chemotherapy pre-treated patients with EGFR M +NSCLC (cat 3)	Further characterise safety and efficacy of afatinib 40 mg qd in patients pre-treated with chemotherapy	Chemotherapy pre-treated patients with EGFR M +NSCLC (additional characterisation)	Planned	Q4 2017 (planned)

There are no planned post-authorisation efficacy studies for afatinib.

Part VI.2.7 Summary of changes to the RMP over time

Not applicable.

PART VI.3 ABBREVIATIONS

ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EU	European Union
HER	Human Epidermal Growth Factor Receptor
ILD	Interstitial Lung Disease
LVEF	Left Ventricular Ejection Fraction
NSAID	Non-steroidal Anti-Inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
PL	Package Leaflet
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TKI	Tyrosine Kinase Inhibitors