GIOTRIF (Afatinib)
Filmtabletten
ZL-Nr.: 63042

Public Risk Management Plan (RMP) Summary

Document Version: 2.0
Document Date: 18.02.2020
Based on EU RMP version 8.1 (09 OCT 2019)

Boehringer Ingelheim (Schweiz) GmbH
Hochbergerstrasse 60B, Postfach
CH-4002 Basel
www.boehringer-ingelheim.ch

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Giotrif is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of Giotrif in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic.

Boehringer Ingelheim (Schweiz) GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Giotrif.

SUMMARY OF RISK MANAGEMENT PLAN FOR GIOTRIF AFATINIB)

This is a summary of the risk management plan (RMP) for Giotrif. The RMP details important risks of Giotrif, how these risks can be minimised, and how more information will be obtained about Giotrif's risks and uncertainties (missing information).

Giotrif's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Giotrif should be used.

This summary of the RMP for Giotrif should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Giotrif's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Giotrif is authorised as monotherapy for the treatment of:

- Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-naïve adult patients with locally advanced or metastatic non-small cell lung carcinoma (NSCLC) with activating EGFR mutation(s)
- Locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy

(see SmPC for the full indication). It contains afatinib as the active substance and it is given orally (20 mg, 30 mg, 40 mg, and 50 mg film-coated tablets).

Further information about the evaluation of Giotrif’s benefits can be found in Giotrif’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Giotrif, together with measures to minimise such risks and the proposed studies for learning more about Giotrif's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Giotrif is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Giotrif are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Giotrif. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information

PVI.Table 1 Summary of safety concerns

	Interstitial lung disease (ILD)
	Hepatic impairment
	Gastrointestinal perforation
Important potential risks	Decreased left ventricular ejection fraction (LVEF)/heart failure
	Developmental toxicity
	Hypersensitivity reactions
	Poor survival following off-label use in combination with vinorelbine in breast cancer
	Use in combination with chemotherapy
Missing information	None

II.B Summary of important risks

Important identified risk "Interstitial lung disease"	
Evidence for linking the risk to the medicine	ILD is a rare and serious (potentially fatal) adverse event reported with other EGFR TKIs. Reports of suspected cases of ILD, including fatal cases, in patients exposed to afatinib have occurred. Patients with a history of current ILD were excluded from participation in clinical trials.
Risk factors and risk groups	Cancer chemotherapy is commonly associated with acute diffuse alveolar damage (i.e. damage of the hollow cavities in the lung tissue, where gas is exchanged with the blood). Furthermore, a combination of drugs with or without radiotherapy can increase the risk of ILD. Smoking history and pre-existing ILD are also risk factors.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Prescription-only medicine. Treatment should be initiated and supervised by a physician experienced in the use of anticancer therapies.
Additional pharmacovigilance activities	None.

Important identified risk "Hepatic impairment"	
Evidence for linking the risk to the medicine	Liver toxicity (hepatotoxicity), including liver failure, has been observed with EGFR TKIs; a background risk of liver toxicity including liver metastases needs to be considered.
Risk factors and risk groups	Clinical trial data indicate that patients with impaired hepatic function at baseline had an increased likelihood of experiencing elevations of liver enzymes (alanine aminotransferase or aspartate aminotransferase) or an adverse event of hepatic impairment.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 4 Prescription-only medicine. Treatment should be initiated and supervised by a physician experienced in the use of anticancer therapies.
Additional pharmacovigilance activities	None.

Important identified risk "Gastrointestinal perforation"	
Evidence for linking the risk to the medicine	Gastrointestinal perforation is an uncommon class effect for EGFR TKI inhibitors. The incidence in patients that were enrolled in randomised controlled trials and in post-marketing experience is very low. In the majority of the reported cases with events of GI perforation, there were confounding factors and alternative explanations for these events.
Risk factors and risk groups	Risk factors for GI 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.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Prescription-only medicine. Treatment should be initiated and supervised by a physician experienced in the use of anticancer therapies.
Additional pharmacovigilance activities	None.

Important potential risk "Decreased LVEF/heart failure"	
Evidence for linking the risk to the medicine	Drugs that inhibit the human EGFR 2 (HER2), such as the monoclonal antibody trastuzumab, have adverse effects on the hearth. Since afatinib acts via a similar mechanism (EGFR/HER2 TKI), its cardiac safety profile has to be carefully assessed. Care has been taken to monitor for the potential cardiac side effects in afatinib trials. Monitoring LVEF at baseline and at routine intervals has been required in all afatinib clinical trials. However, only in circumstances in which life expectancy is estimated to be of short duration, regular monitoring of LVEF may be reconsidered, based on the risk-benefit assessment and with the full awareness of the patient and investigator.
Risk factors and risk groups	Patients treated with long-term cancer therapy including prior chemotherapy; patients with history of significant cardiac diseases, vascular disorders, and also concurrent with other risk factors such as hypertension, diabetes, hyperlipidaemia, smoking, etc.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 4 Prescription-only medicine. Treatment should be initiated and supervised by a physician experienced in the use of anticancer therapies.
Additional pharmacovigilance activities	None.

Important potential risk "Developmental toxicity"	
Evidence for linking the risk to the medicine	Based on the mechanism of action, Giotrif has the potential to cause foetal harm. The embryo-foetal development studies performed with afatinib in rats and rabbits revealed no indication of teratogenicity up to dose levels including maternal death. The identified changes were restricted to skeletal alterations consisting of incomplete ossifications/unossified elements (rat) and abortions at maternally toxic dose, reduced foetal weights, as well as mainly visceral and dermal variations (rabbit).
Risk factors and risk groups	No specific data/information has been found regarding risk groups or risk factors related to developmental toxicity in pregnant women (or more globally in patients) with lung cancer. Due to the indication, the patient population is expected to be rather old and beyond fertile age (mean age of about 60 years), which reduces the risk of an exposure of women of childbearing potential.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Prescription-only medicine. Treatment should be initiated and supervised by a physician experienced in the use of anticancer therapies.
Additional pharmacovigilance activities	None.

Important potential risk "Hypersensitivity reactions"	
Evidence for linking the risk to the medicine	Hypersensitivity reactions were considered a potentially clinically important adverse event, with allergic reactions cited as uncommon adverse events during the use of the EGFR TKI gefitinib. In addition, covalent binding to albumin (a blood protein) has been observed for other drugs used in oncology (chlorambucil, melphalan, and others, and penicillins); the presence of covalently modified blood proteins may constitute a possible risk for immune reaction-based AEs.
Risk factors and risk groups	Risk groups or risk factors are unknown.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3. PL section 2 Prescription-only medicine. Treatment should be initiated and supervised by a physician experienced in the use of anticancer therapies.
Additional pharmacovigilance activities	None.

Important potential risk "Poor survival following off-label use in combination with vinorelbine in breast cancer"	
Evidence for linking the risk to the medicine	In a clinical trial (LUX-Breast-1) investigating the efficacy and safety of afatinib+vinorelbine vs. trastuzumab+vinorelbine in patients with HER2-positive metastatic breast cancer after failure of trastuzumab-containing regimen, the overall survival was shorter for afatinib+vinorelbine compared to trastuzumab+vinorelbine. Because afatinib is an antineoplastic agent, off-label use of afatinib outside oncology indications is considered highly unlikely. Given the availability of several approved therapies for HER2 positive metastatic breast cancer (e.g. trastuzumab, pertuzumab, lapatinib, trastuzumab-emtansine), the likelihood of physicians using afatinib either alone or in combination with vinorelbine, without regulatory approval is considered low, especially when considering the poor survival data and negative benefit/risk profile for the combination. However, the spontaneous reports of off-label use in breast cancer support that such use can occur. As vinorelbine is both active and approved in the treatment of NSCLC, use of afatinib in combination with vinorelbine could be anticipated. There is no published evidence for clinical efficacy with the combination of afatinib plus vinorelbine in EGFR M+NSCLC and the risk for off-label use of this combination is considered low.
Risk factors and risk groups	Patients outside the authorised indication.
Risk minimisation measures	Prescription-only medicine. Treatment should be initiated and supervised by a physician experienced in the use of anticancer therapies.
Additional pharmacovigilance activities	None.

Important potential risk "Use in combination with chemotherapy"	
Evidence for linking the risk to the medicine	Because afatinib is an antineoplastic agent, off-label use of afatinib outside oncology indications is considered highly unlikely. In the EU, afatinib is approved as a monotherapy for treatment of patients with EGFR M+ NSCLC not previously treated with EGFR TKI. In patients who have previously received EGFR TKIs (gefitinib, erlotinib), afatinib also showed activity when used in combination with paclitaxel or with cetuximab, although afatinib has not been approved for combination use with these products. The likelihood of physicians using afatinib without regulatory approval is considered low.
Risk factors and risk groups	Patients outside the authorised indication.
Risk minimisation measures	Prescription-only medicine. Treatment should be initiated and supervised by a physician experienced in the use of anticancer therapies.
Additional pharmacovigilance activities	None.

Missing information	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

There are no studies which are conditions of the marketing authorisation or specific obligation of Giotrif.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Giotrif.