PART VI.2 ELEMENTS FOR A PUBLIC SUMMARY

Part VI.2.1 Overview of disease epidemiology

Lung cancer is the leading cause of cancer deaths in men and the second leading cause of cancer deaths in women. In 2012, there were about 310 000 newly diagnosed lung cancer (all types) cases in the 27 European Union countries.

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases. At diagnosis, 10-15% of patients have locally advanced cancer (stage IIIB), and 40% of patients have metastatic cancer (stage IV).

In European countries in 2012, about 56-63% (i.e. 173 400 to 195 000) of all new lung cancer cases were diagnosed with advanced stage NSCLC. Of these, 62 400 to 70 200 were diagnosed with the adenocarcinoma subtype.

The prognosis for advanced NSCLC has not changed significantly in the past decades. With an overall 5-year survival rate of 16-19%, the treatment of NSCLC remains a major clinical challenge.

Part VI.2.2 Summary of treatment benefits

VARGATEF® is intended for use in combination with docetaxel to treat adult patients with locally advanced, metastatic or recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy.

In the pivotal study 1199.13, patients with tumours of different histology were included; of them, 652 patients (320 with adenocarcinoma) received VARGATEF® in combination with docetaxel and 655 patients (333 with adenocarcinoma) received placebo with docetaxel. The primary endpoint was the progression-free survival, i.e. the length of time that a patient lives with cancer but it does not get worse upon VARGATEF® treatment. The key secondary endpoint was the overall survival, i.e. the length of time that patients remain alive from the start of VARGATEF® treatment.

VARGATEF® significantly reduced in adenocarcinoma patients the risk of tumour progression or death by 23%; the risk of death was significantly reduced by 17%. The progression-free survival was extended with VARGATEF® treatment from 2.8 months to 4.2 months. The overall survival was extended from 10.3 months to 12.6 months. In addition, disease control and tumour shrinkage were significantly improved with VARGATEF® treatment, with the greatest improvement seen in patients with adenocarcinoma.

Part VI.2.3 Unknowns relating to treatment benefits

In the pivotal trial 1199.13 and the supporting trial 1199.14, VARGATEF® exerted a clinically relevant treatment benefit, in particular in patients with second line advanced or recurrent non-small cell lung cancer of adenocarcinoma histology; there is no data to suggest that the effectiveness of VARGATEF® would be different across other patient subpopulations defined by age, gender, race, geographical region, smoking status.

Part VI.2.4 Summary of safety concerns

PVI.Table 5 Important identified risks

Risk	What is known	Preventability
Diarrhoea	In the pivotal Phase III trial in VARGATEF® plus docetaxel (trial 1199.13), patients on VARGATEF® were more likely to experience diarrhoea than patients on placebo. The majority of diarrhoea events were of mild to moderate severity, and manageable with using smaller doses of VARGATEF® and the use of anti-diarrhoeal drugs, such as loperamide.	Management should start at the first signs of diarrhoea. This includes adequate intake of fluids and electrolytes (to prevent or treat dehydration) and of anti- diarrhoeal drugs. Patients with severe diarrhoea may need to stop or use smaller doses of VARGATEF®. Recommended dose reductions for VARGATEF® are provided in the summary of product characteristics (SmPC).
Liver enzyme elevations and abnormally high bilirubin blood levels (hyperbilirubinaemia)	In trial 1199.13, liver enzyme elevations occurred more often in patients treated with VARGATEF® and docetaxel than in those treated with placebo and docetaxel. Most elevations were of mild or moderate severity, returned to normal in the majority of patients, and did not lead to apparent liver disease.	Liver enzyme increases in clinical trials with VARGATEF® mostly returned to normal when VARGATEF® treatment was interrupted. Liver enzymes and bilirubin levels need to be closely and periodically monitored after start of VARGATEF® therapy. If relevant liver enzyme elevations are measured, interruption of treatment followed by use of smaller doses or completely stopping VARGATEF® treatment should be considered. Recommended dose reductions for VARGATEF® are provided in the SmPC.
Abnormally low level of white blood cells (neutropenia)	In trial 1199.13 more patients treated with VARGATEF® and docetaxel had neutropenia with or without fever, than those treated with placebo and docetaxel. Neutropenia is a known side effect of docetaxel.	Blood counts should be checked during therapy, in particular during the combination treatment with docetaxel. Recommended dose reductions for VARGATEF® are provided in the SmPC.
Bacterial infection in the bloodstream (sepsis)	In trial 1199.13 patients treated with VARGATEF® and docetaxel had more sepsis than those treated with placebo and docetaxel. Sepsis is a known side effect of docetaxel.	Sepsis has been observed as a complication of neutropenia. Blood counts should be checked during therapy, in particular during the combination treatment with docetaxel. Recommended dose reductions for VARGATEF® are provided in the SmPC.
Venous thromboembolism (VTE)	In trial 1199.13, patients on VARGATEF® and docetaxel experienced more VTE, in particular deep vein thrombosis, compared with patients on placebo and docetaxel.	Patients should be closely watched for thromboembolic events. VARGATEF® should be stopped in patients with life-threatening venous thromboembolic reactions.

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

Risk	What is known	Preventability
Perforation (gastro-intestinal and non-gastro-intestinal)	In trial 1199.13 patients treated with VARGATEF® and docetaxel did not have more perforation when compared to patients treated with placebo and docetaxel. Few patients experienced a gastro-intestinal or non-gastro-intestinal perforation.	Patients who had previous abdominal surgery should be treated with particular caution. VARGATEF® should only be started at least 4 weeks after major surgery. VARGATEF® should be permanently stopped in patients who develop gastrointestinal perforation.
Bleeding	In trial 1199.13, the number of patients with adenocarcinoma who experienced bleeding was comparable between the treatment arms. In patients with squamous cell carcinoma, more patients in the VARGATEF® arm experienced bleeding than patients in the placebo arm.	Patients taking blood thinners, such as warfarin or phenprocoumon, should be checked regularly for changes in clotting parameters (e.g. prothrombin time, INR) or clinical bleeding episodes. Patients with brain metastases should be closely watched for signs and symptoms of brain bleeding. Treatment with VARGATEF® is not recommended in patients with recent lung bleeding (>2.5 mL of red blood) and those with centrally located tumours with x-ray evidence of local invasion of major blood vessels or radiographic evidence of cavitary or necrotic tumours.
High blood pressure (hypertension)	High blood pressure is a known side effect of medicinal products belonging to the class of the VEGFR inhibitors. In trial 1199.13 the number of patients who experienced high blood pressure was increased in the VARGATEF® arm compared to the placebo arm, but less frequent than expected with other medicines belonging to the same class as VARGATEF®. Most blood pressure elevations were of mild or moderate severity and resolved in the majority of patients. The number of patients who started a new treatment for high blood pressure during trial 1199.13 was low in the VARGATEF® arm.	Patients on blood pressure-lowering medication should have their blood pressure measured at regular intervals as indicated by their hypertensive disease. All patients should have routine blood pressure measurements as clinically indicated.

PVI.Table 6 Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
Arterial thromboembolism (ATE)	Arterial thromboembolism is a known effect of treatment with medicinal products belonging to the class of the VEGFR inhibitors. There is no evidence of an increased frequency of ATE in NSCLC patients based on data collected in trial 1199.13. However, in patients suffering from idiopathic pulmonary fibrosis (IPF), ATE occurred more frequently in patients treated with VARGATEF® than in those who received placebo. The IPF patient population has different medical history and risk factors as compared to patients with NSCLC.
Treatment in pregnant women and teratogenicity	VARGATEF® has not been investigated in pregnant women. The properties of VARGATEF® suggest a potential adverse effect on the embryo/foetus that was confirmed in a non-clinical study. Therefore, as a precaution, women should not be treated with VARGATEF® during pregnancy unless the clinical condition requires treatment. Women of childbearing potential being treated with VARGATEF® should be advised to avoid becoming pregnant while receiving treatment with VARGATEF® and to use adequate contraception during and at least 3 months after the last dose of VARGATEF®.
Liver dysfunction	Alterations of liver laboratory values have been observed in patients treated with VARGATEF®. Liver enzyme increases in clinical trials with VARGATEF® mostly returned to normal when VARGATEF® treatment was interrupted. However, it cannot be excluded that particular patient may develop liver dysfunction (hepatic failure).
Heart problems (cardiac failure)	Some medicines belonging to the same class as VARGATEF® may cause heart problems such as heart failure or congestive heart failure. In trial 1199.13, very few patients experienced cardiac failure in both the placebo and the VARGATEF® study arm. Cardiac failure was not reported in patients with adenocarcinoma.
Abnormal ECG heart tracing (QT prolongation)	Abnormal heart tracing (so-called QT prolongation) has been observed with some medicines belonging to the same class as VARGATEF®. However, there is no evidence that VARGATEF® increase the risk for QT prolongation based on non-clinical studies, based on a dedicated study in patients with renal cell cancer, based on study 1199.13 in patients with NSCLC.

PVI.Table 7 Missing information

Missing information	What is known
Treatment in breastfeeding women	VARGATEF® has not been investigated lactating women. Pre-clinical studies showed that small amounts of nintedanib and its metabolites were secreted into milk of lactating rats. Therefore, as a precaution, breastfeeding should be discontinued during treatment with VARGATEF®.
Treatment in patients with hepatic impairment	Most patients in the clinical trial programme in oncology had normal hepatic function (81.5%) or mild hepatic impairment (14.9%). Patients with total bilirubin above upper limit of normal (ULN), and/or alanine aminotransferase (ALT) >1.5x ULN, and/or aspartate aminotransferase (AST) >1.5x ULN, were excluded from trial 1199.13. There is insufficient data to evaluate whether there is a risk from VARGATEF® treatment to patients with moderate or severe hepatic impairment. Three Phase I/II studies examined patients with hepatic impairment (1199.37, 1199.39, and 1199.120 – VARGATEF® in patients with advanced hepatocellular carcinoma). The adverse event profile was comparable with that of the overall population of oncology patients exposed to VARGATEF®.
Treatment in patients with renal impairment	Patients with renal impairment (serum creatinine >1.5x ULN) were excluded from the pivotal Phase III trial in NSCLC patients with VARGATEF® + docetaxel. There is insufficient data to evaluate whether there is a risk from VARGATEF® treatment to patients with renal impairment; however, because less than 1% of a single dose of VARGATEF® is excreted via the kidney, a risk to patients with renal impairment is not anticipated.
Treatment in patients with healing wounds	Due to its mode of action, VARGATEF® may impair wound healing. Therefore, patients with major injuries and/or surgery within the 10 days prior to trial randomisation, with incomplete wound healing, were excluded from trial 1199.13. During the trial, 25 patients in the placebo arm and 19 patients in the VARGATEF® arm had surgery; wound healing was not identified as a safety concern. Nevertheless, further data is needed from post-marketing experience to fully exclude this potential safety issue.
Treatment of subpopulations with co-morbid CNS conditions such as dementia, depression, brain metastasis, or with co-morbid conditions such as arthritis and osteoporosis	There is limited information on the safety of VARGATEF® treatment in patients with central nervous system conditions such as dementia, depression, brain metastasis, or in other conditions such as arthritis and osteoporosis.
Treatment of patients weighing <50 kg	In study 1199.13 there was a higher frequency of SAEs in patients weighing <50 kg treated with VARGATEF® plus docetaxel compared to patients weighing ≥50 kg. However, the number of patients with a body weight <50 kg was small and therefore insufficient to evaluate whether there is a risk from VARGATEF® treatment in this population.
In vitro inhibitory potential on organic anion transporter (OAT)1 and OAT3	Laboratory investigations are currently ongoing to evaluate whether nintedanib might inhibit some proteins that are responsible for the transport of substances in the kidney.

Part VI.2.5 Summary of 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 these risks. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures. The SmPC and the package leaflet for VARGATEF® can be found on the VARGATEF®'s EPAR page.

This medicine has no additional risk minimisation measures.

Part VI.2.6 Planned post-authorisation development plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports[3]
1199.37: A multicentre, open label, phase I/randomised phase II study to evaluate safety, pharmacokinetics and efficacy of BIBF 1120 in comparison with sorafenib for advanced hepatocellular carcinoma patients (category 3)	Phase I: maximum tolerated dose (MTD) in patients with mild and moderate liver impairment and recommended dose for phase II Phase II: efficacy and safety of nintedanib as compared to sorafenib in patients with HCC	Treatment of patients with hepatic impairment	Started	The final CTR including the PK analyses of patients of Group 1 and 2* is expected in Q1 2015.
1199.39: A multicenter, open label, phase I/randomized phase II study to evaluate safety, pharmacokinetics and efficacy of BIBF 1120 in comparison with sorafenib for advanced hepatocellular carcinoma patients in Asia (category 3)	Phase I: MTD in patients with mild and moderate liver impairment and recommended dose for phase II Phase II: efficacy and safety of nintedanib as compared to sorafenib in patients with HCC	Treatment of patients with hepatic impairment	Started	The final CTR including the PK data for the patients of Group 1 and 2* will be available by Q1 2015.
1199.120: An open label, dose escalation phase I study to evaluate the safety and tolerability of continuous twice-daily oral treatment of nintedanib in Japanese patients with hepatocellular carcinoma (category 3)	To evaluate MTD in Japanese HCC and to recommend dose of nintedanib for further trials in two groups of patients according to liver function To evaluate PK of nintedanib and to explore a correlation of PK with degree of liver impairment	Treatment of Japanese patients with hepatic impairment	Started	Final data including PK data for the patients of Group 1 and 2* is expected for Q4 2015. The final CTR is projected for Q1 2016.
PK1407T: *In vitro* evaluation of the interaction of nintedanib with human OAT transporters (category 3)	To determine the interaction potential of BIBF 1120 toward OAT1 and OAT3	*In vitro* inhibitory potential on OAT1 and OAT3	Started	The final CTR is expected by end of 2014

* Group I included patients with AST and ALT ≤2xULN and Child Pugh A (score 5-6) at baseline. Group II included patients with AST or ALT >2xULN to ≤5xULN or Child Pugh B (score 7 only) at baseline

Studies which are a condition of the marketing authorisation

None of the above listed studies is a condition of the marketing authorisation.

Part VI.2.7 Summary of changes to the risk management plan over time

Not applicable.