VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Lung cancer is a type of cancer that begins in the lungs; two spongy organs in the chest that take in oxygen when you inhale and release carbon dioxide when you exhale (7). Lung cancer is the leading cause of cancer deaths worldwide, among both men and women. Every year, two to 80 per 100,000 people develop lung cancer (11). The median age at diagnosis is around 70 years (10).

People who smoke have the greatest risk of developing lung cancer, accounting for 80-85% of lung cancer cases (9, 11), although other risk factors (*e.g.* exposure to asbestos) are also known (10). Signs and symptoms of lung cancer may include a new cough that doesn't go away, coughing up blood, shortness of breath, chest pain, hoarseness, losing weight without trying, and bone pain (7).

Around 85% of all lung cancers are classified as non-small cell lung cancer. This type of lung cancer is mostly diagnosed at a later stage, called locally advanced or metastatic (when cancer cells have spread from the original site to other parts of the body) (3, 12). The stage of non-small cell lung cancer plays an important role in determining which type of treatment should given (8).

VI.2.2 Summary of treatment benefits

Gefitinib is used to treat adults who have non-small cell lung cancer of a late stage (locally advanced or metastatic). It is used in patients whose cancer cells have an alteration (mutation) in a protein that is involved in cell growth, called EGFR.

Current treatment strategies for this specific type of lung cancer (called EGFR mutation-positive locally advanced or metastatic non-small cell lung cancer) include (5, 6):

- Chemotherapy with anticancer medications that block the protein EGFR. These medications are called first-generation (*e.g.* gefitinib, erlotinib) or second-generation EGFR tyrosine kinase inhibitors (*e.g.* afatinib);
- Surgery and/or treatment with radiation.

The efficacy of gefitinib has been studied in several studies:

- In one main study involving 1,217 adult patients with late stage non-small cell lung cancer, gefitinib was compared with a drug combination of carboplatin and paclitaxel (other anticancer medicines). The study included patients with and without the EGFR mutation. Gefitinib was more effective at preventing the cancer from worsening than the combination. Among patients with the EGFR mutation, those who took gefitinib lived for an average of nine and a half months without the disease getting worse, compared with about six months for those who took the drug combination therapy (3).
- In a second main study involving 1,466 patients with late stage non-small cell lung cancer, gefitinib was compared with docetaxel (another anticancer medicine). This study also included patients with and without the EGFR mutation. Patient survival among all patients who took gefitinib was similar to those who took docetaxel, but patients were feeling better with gefitinib (3).

VI.2.3 Unknowns relating to treatment benefits

There is not enough information available regarding the use of gefitinib:

- In children and adolescents aged less than 18 years. However, children and adolescents usually do not get non-small cell lung cancer. Gefitinib should not be used in children and adolescents;
- In women who are pregnant or who are breast-feeding;
- In patients with severe kidney problems (creatinine clearance ≤ 20 ml/min).

VI.2.4 Summary of safety

concerns Important identified risks

Risk	What is known	Preventability
Continuation of gefitinib as additional treatment to chemotherapy when gefinitib is not effective anymore	Most tumours eventually develop resistance to gefitinib treatment, meaning that gefitinib is not effective anymore in stopping the cancer from growing. Mostly, the cancer progresses after around one year of treatment with gefitinib.	Gefitinib should not be used in combination with other medicines to treat non-small cell lung cancer of a late stage.
Bleeding (haemorrhagic events)	Up to one in 10 patients treated with gefitinib may experience bleeding, such as nosebleed [epistaxis] or blood in urine [haematuria].	Nothing proposed.
Inflammation of the liver (hepatitis)	Liver function tests may be abnormal in more than one in ten patients treated with gefitinib. Up to one in 100 patients treated with gefitinib may develop hepatitis. There are only a few reports of liver failure during gefitinib treatment which, in some cases, led to death.	Doctors should perform regular liver function tests. Doctors should use gefitinib with caution in patients who show mild to moderate changes in liver function. Doctors should consider discontinuation of gefitinib treatment when changes in liver function are severe.

Risk	What is known	Preventability
Inflammation of the lung (interstitial lung disease)	Interstitial lung disease is a side effect that has been commonly observed during treatment with gefitinib. Around one in 100 patients treated with gefitinib may develop the disease, and it is often severe. Some fatal cases have been reported. In a study, the increased risk of interstitial lung disease was especially seen during the first four weeks of treatment with gefitinib. Risk of severe complications of the disease was higher in older patients, patients who smoked, had reduced normal lung, or pre-existing interstitial lung disease.	If patients experience worsening of breathing tract symptoms such as shortness of breath, cough and fever, they should inform the doctor. The doctor should interrupt treatment with gebitinib and promptly investigate the patient. If interstitial lung disease is confirmed, gefitinib should be discontinued and the patient should be treated appropriately.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Events that concern the blood vessels and blood supply of the brain (cerebrovascular events)	Currently, available data contains insufficient information to establish a causal relationship with gefitinib.
Drug interactions	Some medicinal products (*e.g.* phenytoin, carbamazepine, rifampicin, barbiturates or herbal products containing St John's wort/*Hypericum perforatum*) may **lower** gefitinib levels in the blood, because they activate the compounds that break down gefitinib. These medications should not be taken together with gefitinib. Other medicinal products (*e.g.* proton-pump inhibitors, H_2-blockers such as ranitidine, antacids) may also **lower** gefinitib levels in the blood, because they reduce acids in the stomach. These medicines can make gefitinib less effective. Some medicinal products (*e.g.* ketoconazole, posaconazole, voriconazole, protease inhibitors, clarithromycin, telithromycin) may **increase** gefitinib levels in the blood, because they block the compounds that break down gefitinib. Especially when starting treatment with these medications, doctors should closely monitor patients for adverse reactions.

Risk	What is known (Including reason why it is considered a potential risk)
	Some patients who were treated with gefitinib and warfarin experienced bleeding; patients taking both medications should be monitored regularly by their doctor for bleeding risk. When gefitinib is taken together with vinorelbine, gefitinib may enhance the suppressing effect of vinorelbine on white blood cell levels; white blood cell levels may be lowered even more.
Events that are resembling signs and symptoms of leukemia (leukaemia-type events)	Currently, available data contains insufficient information to establish a causal relationship with gefitinib.
Tumour bleeding (tumour haemorrhage)	Currently, available data contains insufficient information to establish a causal relationship with gefitinib.

Missing information

Risk	What is known
Use during pregnancy and breast-feeding (lactation)	There is no information regarding the use of gefitinib in pregnant women. Studies in animals have shown toxic effects of gefitinib on rat pups when gefitinib is given to the mother pup during pregnancy and birth, but the risk for humans is unknown. Women should avoid becoming pregnant during treatment with gefitinib. Women should not be treated with gefitinib while they are pregnant unless clearly necessary. It is unknown if gefitinib is excreted in human milk. Gefitinib was observed in milk of breast-feeding rats. Women should not take gefitinib while breast-feeding. Women should stop breast-feeding during treatment with gefitinib.
Use in patients with severe kidney problems	There is not enough information available regarding the use of gefitinib in patients with severe kidney problems (creatinine clearance ≤ 20 ml/min). Doctors should be careful when treating patients with severe kidney problems with gefitinib.

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

No additional risk minimisation measures have been proposed.

VI.2.6 Planned post authorisation development plan

No post-authorization development is planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.