VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Non-Small Cell Lung Cancer (NSCLC):

Non-small cell lung cancer accounts for 85–90% of lung cancers [Reck, 2014] and is the leading cause of cancer-related mortality around the world [Molina, 2008]. It is estimated that 221,200 new cases of lung cancer would be detected in 2015. Cigarette smoking is the most important risk factor for lung cancer. Survival rates at 5-years for NSCLC have been observed to be 21%.[ACS, 2015]. The average lifetime chance that a man will develop lung cancer is about 1 in 13. For a woman it is about 1 in 16. These numbers include both smokers and non-smokers. Lung cancer occurs mainly in older people. It is rare in people under the age of 45 [ACS, 2015].

Pancreatic cancer: (cancer of pancreas-organ located behind the stomach and infront of the spine):

Although the frequency of this disease is lower than many other types of cancer, pancreatic cancer has high mortality and is amongst top 5 causes of death from cancer [Yadav, 2013]. Pancreatic cancer is the eighth most common cancer in women and fourth leading cause of cancer death in men and women [ASCO, 2015]. Less than 10% of cases of pancreatic cancer occur among individuals younger than 55 years old, and the average onset age is 71 years. 25% of pancreatic cancer cases are due to smoking. Recent studies concluded that heavy drinkers might have an increased risk of pancreatic cancer and all pancreatic disorders affect Blacks more than any other race [Yadav, 2013]. The occurrence of pancreatic cancer is around nine times higher in people aged 80–84 years compared to 50–54 years and less than 10% of cases occur in people under 50 years [Creighton, 2010].

VI.2.2 Summary of treatment benefits

Erlotinib is approved for first line treatment of patients with metastatic (spread of cancer from the part of the body where it started (the primary site) to other parts of the body) NSCLC. Erlotinib is approved for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy (cancer treatment with chemical substances). Erlotinib is approved for treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Erlotinib hydrochloride in combination with gemcitabine for the treatment of patients with locally advanced, unresectable (non removable) or metastatic pancreatic carcinoma (cancer) [NCI, 2013]. Erlotinib improves the cytotoxic effects of chemotherapy in preclinical (animal study) models. So, it was proposed that combination of erlotinib and chemotherapy could further improve outcome of chemotherapy in patients with advanced NSCLC [Wang, 2012]. Erlotinib not only improves survival in previously treated patients with NSCLC, but also improves tumor-related symptoms and important aspects of quality of life [Bezjak, 2007]. Never smokers experienced an improvement in survival when treated with erlotinib and chemotherapy [Herbst, 2005]. In advanced clinical trials, erlotinib provides an evidence of disease control for the treatment of central nervous system tumors (abnormal growth of organ or tissue) called gliomas out of which 55% are glioblastoma multiforme [Halatsche, 2006].

VI.2.3 Unknowns relating to treatment benefits

There have been no specific studies in elderly patients regarding treatment with erlotinib. The efficacy of erlotinib in patients under the age of 18 years has not been established.There are no adequate data for the use of erlotinib hydrochloride in pregnant and lactating women. The safety and efficacy of erlotinib has not been studied in patients with severe hepatic dysfunction; thus its use is not recommended in these patients.

VI.2.4 Part VI.2.4 Summary of safety concerns

Table 5-5 Important identified risks

Risk	What is known	Preventability
Drug induced skin toxicity (Cutaneous toxicity)	Bullous, blistering and exfoliative (peeling) skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis (flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters), which in some cases were fatal (causing death). Signs and symptoms include rash which may occur or worsen in sun exposed areas, itching, dry skin and loss of hair, inflammatory reactions around the fingernail, infection of hair follicles, acne, cracked skin (skin fissures), eyelash changes, excess body and facial hair of a male distribution pattern, eyebrow changes, brittle and loose nails, flushed or painful palms or soles, severe blistering or peeling of skin (suggestive of Stevens-Johnson syndrome).	Patient is advised not to take erlotinib hydrochloride if allergic to erlotinib or any of the ingredients of this medicine. The patient should immediately inform the physician if he/she develops severe blistering or peeling of skin as the physician might need to interrupt or stop the patient's treatment with erlotinib hydrochloride.. Patients with bullous (a large blister containing serous fluid) and exfoliative skin disorders should be tested for skin infection and treated accordingly. If exposed to sun, protective clothing, and/or use of sun screen (e.g. mineral-containing) may be advisable.
Group of lung diseases affecting the tissue and space around the air sacs of the lungs (Interstitial Lung Disease)	Erlotinib hydrochloride causes interstitial lung disease which is a form of lung irritation due to development of scars and inflammation of the lungs. It is uncommon in European patients (affecting up to 1 in 100 people) and common in Japanese patients (affecting up to 1 in 10 people). This risk can worsen your present medical condition and can have fatal (causing death) outcomes in some cases. Signs and symptoms include sudden difficulty in breathing associated with cough or fever.	Physician should be informed if patient observes any of the signs and symptoms so that the physician may permanently stop the treatment with erlotinib hydrochloride and start treatment with some other medicines.

Risk	What is known	Preventability

Liver injury	Rare cases of liver failure have been reported due to the use of erlotinib hydrochloride and affect 1 in 1,000 patients. Signs and symptoms of liver failure include: Loss of appetite, decreased weight, abnormal blood tests for the liver function.	Physician should be informed regarding history of any severe liver disease as treatment with erlotinib hydrochloride is not recommended in patients with liver diseases. Before taking erlotinib hydrochloride, physician should be informed regarding the presence of any glucuronidation (a detoxification process in liver) disorder like Gilbert's syndrome (condition characterized by periods of elevated levels of a toxic substance called bilirubin in the blood).
		Liver functions should be continuously monitored. If blood test indicates severe changes in the liver function, then treatment with erlotinib hydrochloride should be interrupted. Patient should be advised to contact physician immediately if patient had abnormal blood tests for the liver function as the physician might reduce the dose or interrupt the treatment of erlotinib hydrochloride.
Fluid loss via stomach and intestines (Gastrointestinal fluid loss)	Erlotinib hydrochloride causes gastrointestinal fluid loss in the form of diarrhea and vomiting which is very common and affects 1 in 10 patients. Persistent and severe diarrhea may lead to low blood potassium levels and impairment of your kidney function, particularly if you receive other chemotherapy treatments at the same time. Signs and symptoms include diarrhea, vomiting, nausea, stomach pain, indigestion, flatulence, and low	The physician should be informed immediately if the patient suffers from any of the mentioned symptoms, as the physician may need to interrupt erlotinib hydrochloride treatment and the patient should be treated in the hospital by rehydrating (process of restoring lost water to the body tissues and fluids) the patient intravenously. Inform the physician if patient suffers from diarrhea as the physician may need to treat with anti-diarrheal drugs (loperamide).

Risk	What is known	Preventability
	potassium levels in the blood.	Renal (kidney) functions and serum electrolytes including potassium levels should be monitored in patients who are at risk of dehydration/fluid loss.

Hole that develops all the way through the stomach, large bowel, or small intestine (Gastrointestinal perforation)	Patients receiving erlotinib hydrochloride are at increased risk of developing gastrointestinal perforation. It is uncommon and may affect 1 in 100 patients. Signs and symptoms include severe pain in abdomen.	Erlotinib hydrochloride should be permanently discontinued in patients who developed gastrointestinal perforations. Physician may need to stop the treatment with erlotinib hydrochloride if patient had severe pain in abdomen. Before taking erlotinib hydrochloride, inform the physician regarding history of peptic ulcers (stomach ulcers) or diverticular disease (a condition in which muscle spasm in the colon (lower intestine) in the presence of diverticula (pouches formation in the wall of the large intestine) causes abdominal pain and disturbance of bowel function without inflammation.) as this may increase the risk gastrointestinal perforation.
Ocular (eye) toxicity	Ocular toxicity is very common and may affect 1 in 10 patients. Signs and symptoms of ocular toxicity includes acute or worsening redness and pain in the eye, increased eye watering, blurred vision and/or sensitivity to light, Inflammation of the colored part of the eye, perforation or ulceration of the cornea (open sore in the outer layer of the cornea).	Before taking erlotinib hydrochloride, inform the physician if patient uses contact lenses and/or have a history of eye problems such as severe dry eyes, inflammation of the front part of the eye (cornea) or ulcers involving the front part of the eye. While using erlotinib hydrochloride, patient should immediately inform the physician if patient had acute or worsening redness and pain in the eye, increased eye watering blurred vision and/or sensitivity to light is developed as it requires urgent treatment. Immediately consult the physician if patient is suffering from eye irritation due to

Risk	What is known	Preventability
		conjunctivitis (inflammation of the conjunctiva of the eye) or keratoconjunctivitis (inflammation of the cornea and conjunctiva) and keratitis (inflammation of the cornea).

Interaction with drugs that either increase or decrease the activity of the proteins [enzyme CYP3A4] which breaks down erlotinib (Interaction with potent inducers and inhibitors of CYP3A4)	Medicines such as antifungals like ketoconazole, protease inhibitors, erythromycin, clarithromycin, phenytoin, carbamazepine, barbiturates, rifampicin, ciprofloxacin, omeprazole, ranitidine, St. John's Wort or proteasome inhibitors, may reduce the efficacy or increase the side effects of erlotinib or may result in low efficacy.	Patient should inform the physician regarding the simultaneous use of erlotinib hydrochloride with these medicines as their simultaneous use should be avoided and the doctor might need to adjust the treatment. Doctor might avoid treating the patient with these medicines while receiving erlotinib hydrochloride.
Interaction with medicines that change the pH [scale that measures how acidic or basic a substance is] of the stomach (Interaction with medicinal products that alter pH of the upper gastrointestinal tract)	Medicinal products that alter the pH of the upper gastrointestinal tract, like proton pump inhibitors (medicines that reduce the amount of acid made by the stomach), H2 antagonists (group of medicines that reduce the amount of acid produced by the cells in the lining of the stomach) and antacids (substance which neutralizes stomach acidity), may alter the solubility of erlotinib hydrochloride and hence its availability in the body.	Patient should avoid the simultaneous administration of erlotinib hydrochloride with proton pump inhibitors, H2 antagonists and antacids. If the use of antacids is considered necessary during treatment with erlotinib hydrochloride they should be taken at least 4 hours before or 2 hours after the daily dose of erlotinib hydrochloride
Interaction with smoking	Smoking decreases the concentration of erlotinib from blood.	Patient is advised to stop smoking if being treated with erlotinib hydrochloride as smoking could decrease the amount of medicine in the blood.

Table 5-6 Important potential risks

None

Table 5-7 Missing information

Risk	What is known
Use in pregnancy and lactation	There are no adequate data for the use of erlotinib in pregnant women .Patient should be advised to avoid pregnancy while being treated with erlotinib hydrochloride and to use adequate contraception during treatment, and for at least 2 weeks after taking the last tablet. Patient should be advised to inform the
	physician immediately if she became pregnant while being treated with erlotinib hydrochloride, for the physician to decide whether or not to continue the treatment. Patient should be advised to not to breast-feed if being treated with erlotinib hydrochloride. Before taking erlotinib hydrochloride, patient should consult physician for advice if she is pregnant or think that she might be pregnant or are planning to have a baby or breast-feeding.

Use in pediatric population	Studies have not been conducted in patients under the age of 18 years with erlotinib hydrochloride. Thus erlotinib hydrochloride is not recommended for use in pediatric patients.
Use in patients with liver problems (Use in patients with hepatic impairment)	Effect of erlotinib hydrochloride is not known in patients with abnormal functioning of the liver. Thus erlotinib hydrochloride is not recommended for use in patients with severe liver disease. Patient should be advised to contact physician immediately if patient had abnormal blood tests for the liver function as the physician might reduce the dose or interrupt the treatment of erlotinib hydrochloride.

VI.2.5 Part VI.2.5 Summary of risk minimization measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other HCPs with details on how to use the medicine, the risks and recommendations for minimizing 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 minimization measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimization measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in erlotinib hydrochloride's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimization measures are for the following risk:

Table 5-8 Group of lung diseases affecting the tissue and space around the air sacs of the lungs (Interstitial Lung Disease)

Risk minimization measure(s)

Summary description of main additional risk minimization measures:
Erlotinib – Dosing Guidelines & Side-Effect Management Strategies for Health Care Professionals.

Objective and rationale: To minimize the risk of interstitial lung disease while using this medicinal product.

Risk minimization measure(s)

Proposed action: Provision of Erlotinib – Dosing Guidelines & Side-Effect Management Strategies.

This education material will be provided to prescribing physicians to convey the following key messages:

- What is erlotinib used for?
- Dosing guidelines
- Adverse events
- Management of ILD-like events
- Reporting of suspected adverse events or reactions

VI.2.6 Part VI.2.6 Planned post authorization development plan

None

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

Not applicable (first submission)

Summary EU-Risk Management Plan