VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Metastatic (spread of cancer to nearby tissues or to other parts of the body) breast cancer:

Worldwide, breast cancer is the leading cause of cancer death among women, and is thought to cause half a million deaths annually. It is the most frequent cause of cancer death in women in both developing and developed regions. Female breast cancer frequency is strongly related to age, with the highest incidence rates overall being in older women, supporting a link with hormonal status. Risk factors include menopausal state, oral contraceptive use, cigarette smoking, and family history of breast cancer.

Non-microcellular lung cancer:

Non-small-cell lung cancer (NSCLC) (a type of lung cancer) accounts for 80%–85% of all lung cancer cases. Approximately 90% of lung cancers among men and 80% among women are related to smoking. The majority of patients present with advanced disease. The frequency

differs considerably across different countries in Europe. The rates vary from 22 to 63 per 100 000 and from 5 to 33/100 000 per year in men and women, respectively. In most European countries, the frequency continues to rise in women but decreases in men. This trend seems to occur later in Southern and Eastern Europe than in the Northern regions. Central European countries show slightly higher survival compared with other regions. Trends in lung cancer mortality in men have tended to decrease in many European countries during the last two decades, particularly in North and Western Europe. Among women, mortality rates are still increasing in many countries.

VI.2.2 Summary of treatment benefits

Vinorelbine is used alone or in combination with other medications to treat cancer that has spread to nearby tissues or to other parts of the body. Vinorelbine is in a class of medications called vinca alkaloids. It works by slowing or stopping the growth of cancer cells in your body.

Metastatic breast cancer:

20 studies of intravenous vinorelbine have been performed for advanced breast cancer patients. 13 of these studies were in mixed patient population i.e anthracycline-pretreated patients and anthracycline-naive patients, were 494 patients. Those patients reported overall response rates of 14 - 45% and survival times of 58-69 weeks. The remaining 7 studies were only anthracycline- pretreated patients were 339 patients these patients reported response rates of 16 – 64% and survival was 24 – 82 weeks.

Another study conducted to investigate effectiveness in advanced breast cancer. This study included 115 patients who received intravenous vinorelbine and 64 patients who received intravenous melphalan. Of those receiving vinorelbine, 13 of 84 (15.5%) patients with measurable disease achieved an intended response compared to 04 of 46 (8.7%) patients receiving melphalan. Overall survival was 35 weeks for patients receiving vinorelbine compared with 31 weeks for those receiving melphalan. None of the treatment had an adverse effect on quality of life.

Intravenous vinorelbine has also been studied in combination with other agents for the treatment of advanced breast cancer. Total 38 different studies of vinorelbine used with combination of either mitoxantrone; 5-fluorouracil, mitomycin, carboplatin, cisplatin, ifosfamide, paclitaxel, docetaxel, capecitabine, gemcitabine, liposomal doxorubicin involving 1471 patient for the second-line treatment of patients with advanced breast cancer have shown overall response rate 50%; 26-66%; 32-57%; 41%; 49%; 28-36%; 32-61%; 37-59%; 52% and 36% respectively.

Non-microcellular lung cancer:

Studies have demonstrated an improvement in overall survival among the patient with age-range 35 years to 80 years. Cancer was observed in 55% of patients. The stage of cancer was divided based on the stage of cancer i.e IB, IIA, IIB, IIIA, IIIB and IV showed 13%, 29%, 13%, 36%, 4%, and 4% of patients respectively. Among those patient 126 patients received intravenous and 139 received oral vinorelbine/cisplatin. The two groups were comparable with respect to baseline similarities. Mean overall survival (OS) for all patients was 79.0 months and the mean disease- free survival (DFS) was 35.0 months. No statistically significant difference in OS or DFS for patients treated with IV or oral vinorelbine was detected. It was concluded that Intravenous or oral administration of vinorelbine in adjuvant treatment with vinorelbine/cisplatin after surgery for lung cancer appear equally effective in terms of overall and disease-free survival.

VI.2.3 Unknowns relating to treatment benefits

The effectiveness of vinorelbine has not been established in breast feeding females, children and those with carcinogenic potential.

VI.2.4 Summary of safety concerns Important identified risks

Risk	What is known	Preventability

Decrease in production of cells responsible for providing immunity (leukocytes), carrying oxygen (erythrocytes), and/or those responsible for normal blood clotting (thrombocytes) (Bone marrow depression)	The simultaneous use of Vinorelbine Accord and other medicines with known bone marrow toxicity (affecting your white and red blood cells and your platelets) can worsen some of the side effects. Do not use Vinorelbine Accord, if you have a low white blood cell (neutrophil) count, low platelet count or a current or recent (in the past 2 weeks) serious infection. A reduction in a special type of white blood cells, which can result in fever	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before each administration of Vinorelbine Accord, a new blood sample will be taken for analysis of its components. If the results of this analysis are not satisfactory, your treatment may be delayed and further checks made until these values return to normal. Contact your doctor as soon as possible if low count of white blood cells, which may increase the risk of infection and low count of red blood cells (anaemia), which may make you feel tired. As changes in the blood may occur, your doctor may order blood samples to be taken to control this (low count of white blood cells, anaemia and/or low count of blood platelets, influence on the liver- or kidney function and the electrolyte balance in your body).

Infection	Do not use Vinorelbine Accord, if you have a low white blood cell (neutrophil) count or a current or recent (in the past 2 weeks) serious infection. Tell your doctor if you have symptoms of infection (such as fever, shivers, cough). You may experience uncommon side effect like severe sepsis (blood Infection).	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before each administration of Vinorelbine Accord, a new blood sample will be taken for analysis of its components. If the results of this analysis are not satisfactory, your treatment may be delayed and further checks made until these values return to normal. Your doctor must always ensure that you receive the dose that is suitable for your situation. However, you should contact your doctor, the emergency department or your pharmacist if you have any suspicions or if you have symptoms of a potential overdose, such as fever, signs of infection or constipation.

Ulceration to the clear tissue covering the front part of the eye (Corneal ulceration)	Vinorelbine Accord must not get into contact with the eye as there is a risk of severe irritation and even corneal ulceration. If this occurs, immediately rinse the eye with normal saline solution and contact an ophthalmologist	The preparation and administration of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the protection of the environment and, in particular, the protection of the personnel handling the medicines. Personnel must be provided with appropriate handling materials, notably long sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area and collection bags for waste. Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended).
Stomach and intestinal disorder (Gastrointestinal Disorder)	Very frequently it is found that nausea and vomiting and the incidence can also be increased when other chemotherapeutic drugs are used together. Mouth sores which may be painful and	Contact your doctor as soon as possible, if you have any of the side effects like nausea, vomiting, constipation, mouth sores, diarrhoea, inflammation of the pancreas and paralytic intestinal blockage (ileus).

	cause difficulty in swallowing and diarrhoea. Inflammation in the food pipe, can occur and no appetite for food. Infrequently severe diarrhoea is reported. In rare cases of inflammation of the organ that makes hormones, including insulin, and digestive juices have been reported.	
Injection site reaction / Local toxicity	Vinorelbine should only be given intravenously and should not be injected into the spine. It is very important to make sure that the cannula is accurately placed in the vein before the injection is commenced. If vinorelbine infiltrates the surrounding tissue during intravenous administration, a substantial	Contact your doctor as soon as possible, if you have any of the following side effects like pain and/or rash on the injection site, injection site necrosis
	irritation may occur. In this case, the injection should be stopped, the vein flushed with saline solution and the rest of the dose should be administered in another vein. In the event of extravasation, glucocorticoids could be given intravenously to reduce the risk of phlebitis.	

Interaction with other drugs which enhance or inhibit a chemical name CYP3A4 (Interaction with enzyme called CYP3A4 inducers and inhibitors)	Interaction of other medicines which enhance or inhibit the activity of a chemical name CYP3A4 and changes the physical and chemical activity of the body and affects drug entry into body and exit from the body. The simultaneous use of Vinorelbine Accord and other medicines which enhance or inhibit the activity of a chemical name CYP3A4 with known bone marrow toxicity (affecting your white and red blood cells and your platelets) can worsen some of the side effects.	Inform your doctor or pharmacist if you are taking any medicines that make your blood more fluidic (anticoagulants), phenytoin (antiepileptic), antifungal (itraconazole), mitomycin C and lapatinib (anticancer), ciclosporin and tacrolimus (affect your immune system), St. John's Wort (Hypericum perforatum), antibiotics such as rifampicine, erythromycin, clarithromycin, telithromycin; antiviral medicines used for acquired immune deficiency syndrome (AIDS) such as ritonavir (HIV protease inhibitors); verapamil, Quinidine (used for heart problems)

Important potential risks

Risk	What is known
Genetic Toxicity (Genotoxicity)	The drug can cause genetic toxicity, which includes change in the number of structure which hold genes which are not in exact number as they are required. Therefore, men being treated with vinorelbine are advised not to father a child during and for up to 6 months (minimum 3 months) following cessation of treatment. Women of childbearing potential must use an effective method of contraception during treatment and up to 3 months after treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with vinorelbine
Deformity of the fetus (Teratogenicity)	Studies in animals have shown embryotoxicity (toxic effects on embryo in womb) and teratogenicity. On the basis of the results of animal studies and the pharmacological action of the medicinal product, the product is suspected to cause serious birth effects when administered during pregnancy. Vinorelbine is contraindicated in pregnancy. Women should not become pregnant during treatment with vinorelbine. In case of a vital indication a medical consultation concerning the risk of harmful effects for the child should be performed for the therapy of a pregnant patient. If pregnancy should occur during the treatment, the possibility of genetic counselling should be considered

Important missing information

Risk	What is known
Can cause cancer (Carcinogenic potential)	Studies carried out in rats and mice showed negative results but these tests were carried out with small doses.

Use during breast feeding	Do not use Vinorelbine Accord, if you are breast-feeding. It is unknown whether the vinorelbine is excreted in human breast milk. The excretion of vinorelbine in milk has not been studied in animal studies. A risk to the suckling cannot be excluded therefore breast feeding must be discontinued before starting treatment with vinorelbine.
Use in children	Safety and effectiveness of vinorelbine in children have not been determined, hence not advisable to for children.

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.

This medicine has no additional risk minimization measures.

VI.2.6 Planned post authorisation development plan

No studies planned.

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

Version	Date	Safety Concern	Comment
3.0	12-Sep-2016	No changes in safety concerns	RMP has been updated as per Day 50 comments received for Vinorelbine 10 mg/ml concentration for solution for infusion (MRP: PT/H/1300/01/MR) to update SmPC and PIL.

2.0	03-Sep-2014	Following safety concerns are added: Important identified risks: Bone marrow depression • Infection • Corneal ulceration • Gastrointestinal Disorder Injection site reaction / Local toxicity Interaction with CYP3A4 inducers and inhibitors Important potential risks: • Genotoxicity • Teratogenicity Missing information: • Carcinogenic potential • Use in children • Use during breast feeding	The Part VI.2 of the RMP Elements of public summary, with sub headings VI.2.1; VI.2.2 and VI.2.4 i.e Overview of disease epidemiology; Summary of treatment benefit and Summary of safety concerns respectively were abbreviated & provided in lay language.