VI.1 Elements for a public summary

VI.1.1 Overview of disease epidemiology

Squamous cell carcinoma (a type of cancer) affecting the head and throat area, the larynx (voice box), oesophagus (food pipe), cervix (lower end of the womb), vulva (external genital organ of female), penis (external genital organ of male) and skin

Squamous cell carcinoma (SCC) is an uncontrolled growth of abnormal cells arising in the squamous cells, which compose most of the skin's upper layers (the epidermis). SCC is the second most common skin cancer. The incidence of SCC is about 10,000 per year in England and Wales. The incidence is higher in Caucasians. There is a rising incidence with age. Men are more commonly affected, probably because of greater head and neck exposure to ultraviolet radiation (UVR). Other risk factors also include exposure to certain chemicals, low immunity, some type of viral infection and genetic predisposition. For SCC with distant metastases (spread of cancer to other parts of body), the five-year survival rate is poor at around 25-40%.

Hodgkin's disease and other malignant lymphomas, including mycosis fungoides

The two main types of malignant lymphoma are Hodgkin lymphoma (also known as Hodgkin disease) and Non-Hodgkin lymphoma (NHL).

- Hodgkin lymphoma:

  Around 1,800 people were diagnosed with Hodgkin lymphoma in 2011 in the UK, that's around 5 people every day. Hodgkin lymphoma can develop at any age, but there are two peaks in incidence – in young adults, and older men and women. 1 in 10 Hodgkin lymphomas are diagnosed in people aged 75 and over. Around 1 in 5 Hodgkin lymphoma cases occur in children, teenagers and young adults (up to age 24). In Europe, around 4,600 people were estimated to have died from Hodgkin lymphoma in 2012. The UK mortality rate is 19th lowest in Europe for males and 13th highest for females. Worldwide, around 25,500 people were estimated to have died from Hodgkin lymphoma in 2012, with mortality rates varying across the world.

- Non-Hodgkin lymphoma (i.e. other malignant lymphomas, including mycosis fungoides):

  Around 12,200 new cases of Non-Hodgkin lymphoma (NHL) (all subtypes combined) were registered in the UK in 2010, which are around 33 people every day. Around 6 in 10 of all NHL (all subtypes combined) cases are diagnosed in people aged 65 and over. The most common NHL subtype is diffuse large B-cell lymphoma (48% of cases). Marginal zone lymphomas and follicular lymphoma make up 20% and 19% of cases respectively. In Europe, around 37,900 people were estimated to have died from NHL in 2012. The UK mortality rate is 6th highest in Europe for males and 8th highest for females. Worldwide, more than 199,000 people were estimated to have died from NHL (all subtypes combined) in 2012, with mortality rates varying across the world.

Testicular carcinoma (seminomas and non-seminomas);

Around 2,200 men in the UK were diagnosed with testicular cancer in 2011, that's around 6 men every day. Testicular cancer is the 16th most common cancer in men in the UK. Testicular cancer is rare before puberty but is the most common cancer in men aged 25-49 in the UK. In Europe, around 1,600 men were estimated to have died from testicular cancer in 2012. The UK mortality rate is eighth lowest in Europe. Worldwide, around 10,400 men were estimated to have died from testicular cancer in 2012, with mortality rates varying across the world.

Intrapleural palliative treatment of malignant pleural effusions (MPE)

Malignant pleural effusion (excess fluid building around the lung) usually observed during the advanced stage of malignancy. Cancers of lung, breast, ovary, and lymphomas constitute more than 75% of cases of MPE. Metastatic cancer of mucus-secreting glands is the most common cause of MPE. In male patients, lung cancer is the most common cause and in females, breast cancer is the most common cause. The survival in MPE depends on the organ of origin, type and stage of primary tumor and usually ranges from 3 to 12 months. Lung cancer has the shortest, ovarian cancer has the longest, and cancer of unknown primary has an intermediate survival.

VI.1.2 Summary of treatment benefits

Squamous vulvar carcinoma:

Nine patients with age range of 80-90 years and histological diagnosis of recurrence of squamo-cellular vulvar cancer were enrolled in study. Intravenous bleomycin was injected and Electrochemotherapy (ECT) was performed. Response to therapy was evaluated and no peri-operative complications were observed. Evaluation of symptoms showed a significant reduction of pain, bleeding, odour ($p < 0.04$) and urinary discomfort ($p < 0.04$).

Hodgkin's disease and other malignant lymphomas, including mycosis fungoides;

Phase-I and Phase-II evaluation of intravenous bleomycin (BLM) in 176patients with lymphomas and/or solid tumors was carried out. The observed side effects were sclerotic changes of the skin of hands (88%), skin hyperpigmentation (78%), fever (70%), loss of hair (68%), inflammation of mouth and lips (47%) lung toxicity (42%), gastrointestinal symptoms
(20%). Pulmonary toxicity occurred after 4^{th}weeks and remained unchanged or regressed on discontinuation of therapy.BLM showed significant regression in all types of malignant lymphomas (40%), in epidermoid carcinomas of the head and neck (57%) and of the esophagus (60%).

Testicular carcinoma

43 patients with metastatic germ-cell tumours (tumours that form from reproductive cells) (36 testicular non-seminomas and 7 testicular seminomas) were treated with 2-6 cycles of bleomycin, etoposide and cisplatin (BEP). Forty (93%) are alive, 37 (86%) with no evidence of disease. It is concluded that BEP is a well tolerated and effective first line treatment for patients with metastatic germ-cell tumours.

Malignant pleural effusions:

The safety and efficacy of Bleomycin 60 units and tetracycline (1 g) as treatment for malignant pleural effusion were evaluated in a multicenter, randomized trial. Overall survival did not differ between the Bleomycin (n=44) and tetracycline treatment (n=41) groups. Of patients evaluated

within 30 days of instillation, the recurrence rate was 36% (10/28) with Bleomycin and 67% (18/27) with tetracycline (p=0.023). Toxicity was similar between groups.

VI.1.3 Unknowns relating to treatment benefits

There is insufficient experience with regard to the administration of bleomycin in paediatric patients.

VI.1.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Harmful effects on the lungs (Pulmonary toxicity)	Harmful effects on the lungs are very common side effects to bleomycin therapy which may occur in more than 1 in 10 patients. Pulmonary toxicity is both dose-related and age-related, occurring more frequently in those over the age of 70 and in patients who have received a total dose of more than 400 units. Pulmonary toxicity has also been observed on occasion in young patients receiving low doses.	Do not use Bleomycin, if patient has an acute lung infection or severe lung impairment or a history of lung damage (possibly) induced by bleomycin. If patients are treated with bleomycin, are examined by doctor more often and/or take X-rays of lungs and a regular pulmonary function test should be performed, to monitor the possible adverse effects of bleomycin on the lungs. If any adverse event may occur immediately talk to doctor or hospital pharmacist or nurse.

Risk	**What is known**	**Preventability**
		hospital pharmacist or nurse.
Skin and mucosal lesions	Skin and mucosal lesions are the most common side effects and are observed in up to 50 % of the patients treated. They comprise redness; rash; itching; formation of ulcers, stretch marks and blisters; heavy pigmentation; and tenderness and swelling of the fingertips which may occur in more than 1 in 10 patients.	If any such lesions are observed immediately talk to doctor or hospital pharmacist or nurse.
Various types of allergic reactions (Idiosyncratic reactions with fever and chills)	Various types of allergic reactions are common side effects to bleomycin therapy which may affect up to 1 in 10 patients.	If any adverse event may occur immediately talk to doctor or hospital pharmacist or nurse.
Heart attack (Myocardial infarction)	Heart attack is a rare side effect to bleomycin therapy which may affect up to 1 in 1000 patients.	If any adverse event may occur immediately talk to doctor or hospital pharmacist or nurse.
Stroke (Cerebrovascular insults)	Stroke is a rare side effect to bleomycin therapy which may affect up to 1 in 1000 patients.	If any adverse event may occur immediately talk to doctor or hospital pharmacist or nurse.

Disease of the capillaries and arterioles; severe disease affecting the blood and kidneys and	In rare cases, bleomycin therapy may cause disease of the capillaries and arterioles; severe disease affecting the blood and	If any adverse event may occur immediately talk to doctor or hospital pharmacist or nurse.

Risk	**What is known**	**Preventability**
inflammation of the small and medium-sized arteries in the brain (Thrombotic microangiopathies e.g. haemolytic uraemic syndrome and cerebral arteritis)	kidneys and inflammation of the small and medium-sized arteries in the brain which may affect up to 1 in 1,000 patients.	
Condition following rapid breakdown of tumours (Tumour lysis syndrome)	Like other cytotoxic active substances, bleomycin can trigger tumour lysis syndrome in patients with rapidly growing tumours. In very rare cases, bleomycin therapy may cause rapid breakdown of tumours which may affect up to 1 in 10,000 patients.	Appropriate supportive treatment and pharmacological measures might prevent or alleviate such complications. If any adverse event may occur immediately talk to doctor or hospital pharmacist or nurse.

Harmful effect on the embryo (Reproductive toxicity)	Animal studies have shown that bleomycin can harm the embryo.	Both men and women must take measures to prevent a pregnancy during use of bleomycin, and for up to 6 months after the end of the treatment. If pregnancy occurs during treatment with bleomycin, genetic counseling is recommended. Men who wish to father children in the future should seek advice on storing sperm before starting treatment with bleomycin.

Important potential risks

Risk	**What is known**
Potential to cause cancer (Carcinogenicity)	Animal studies have shown that bleomycin can harm the embryo and can cause cancers of fibrous connective tissues and kidney.

Risk of miscarriage used during the first three months of pregnancy (Risk of abortion when exposed during the first trimester of pregnancy)	The use of bleomycin should be avoided during pregnancy, especially during the first 3 months. If bleomycin treatment is vital during the first three months of pregnancy, a medical consultation on aborting the pregnancy is essential. After the first three months of pregnancy, where treatment can no longer be postponed and the mother still wishes to continue with the pregnancy, chemotherapy can be performed, but only after providing warning of the low risk (yet impossible to rule out) that the child will be malformed.

Missing information

Risk	**What is known**
Use in children (Use in paediatric population)	There is insufficient experience with regard to the administration of bleomycin in children and adolescents.Until paediatric population) more information is available, bleomycin should only be administered in this patient group in exceptional circumstances and at special facilities. If administration is indicated as part of a combination regimen the dosage is usually calculated based on the body surface area and adjusted to meet individual requirements of each patient. Current specialized protocols and guidelines should be consulted for appropriate treatment regimen.

VI.1.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, pharmacists and other health care professionals 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 minimisation measures.

This medicine has no additional risk minimization measures.

VI.1.6 Planned post authorisation development plan

No studies planned.

VI.1.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concern	Comment
2.0	10-Nov-2015	The safety concerns were added/ modified as below: - "Risk of abortion when exposed during the first trimester of pregnancy" is added as important potential risk. - The important potential risks 'Teratogenicity' and 'Mutagenicity' were reclassified as important identified risks under the common term 'Reproductive toxicity'.	The RMP has been updated as per the RMS Day 70 Preliminary Assessment Report of Bleomycin Accord, dated 21-Sep-2015.