VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Malignant Melanoma

Melanoma, also known as malignant melanoma, is a type of cancer that develops from the pigment-containing cells known as melanocytes. Melanomas typically occur in the skin, but may rarely occur in the mouth, intestines or the eye. Malignant melanoma is the ninth most common cancer in Europe, with more than 100,000 new cases diagnosed in 2012 (3% of the total). In Europe (2012), the highest age-standardised numbers of new cases of the disease per year in relation to the population for malignant melanoma are in Switzerland for men and Denmark for women; the lowest numbers are in Albania for both men and women. UK numbers of new cases of the disease per year in relation to the population for malignant melanoma are estimated to be the ninth highest in males in Europe, and seventh highest in females. Malignant melanoma is the 19th most common cancer worldwide, with around 232,000 new cases diagnosed in 2012 (2% of the total). The numbers of new cases of the disease per year in relation to the population for malignant melanoma are highest in Australia/New Zealand and lowest in South Central Asia, but this partly reflects varying data quality worldwide **(Ferlay J *et al*, 2012) (WHO, 2012) (Cancer Research UK. Skin cancer incidence statistics, 2014).**

Hodgkin Lymphoma

Hodgkin lymphoma is an uncommon cancer that develops in the lymphatic system, which is a network of vessels and glands spread throughout your body. The lymphatic system is part of the immune system. Around 17,600 new cases of Hodgkin lymphoma were diagnosed in Europe in 2012 (0.5% of total cancer cases). In Europe (2012), the highest age-standardised numbers of new cases of the disease per year in relation to the population for Hodgkin lymphoma are in Croatia for both men and women; the lowest numbers are in Iceland for men and Albania for women. UK numbers of new cases of the disease per year in relation to the population for Hodgkin lymphoma are estimated to be the 6th highest in males in Europe, and 20th lowest in females. Around 66,000 new cases of Hodgkin lymphoma were diagnosed worldwide in 2012 (0.5% of total cancer cases). The number of new cases of the disease per year in relation to the population for Hodgkin lymphoma are highest in Northern America and lowest in Eastern Asia, but this partly reflects varying data quality worldwide **(Ferlay J *et al*, 2013) (Cancer Research UK. Hodgkin lymphoma, 2014).**

Between 91 and 94 out of every 100 people (91 to 94%) diagnosed with early stage Hodgkin lymphoma (stage 1 or 2 disease) will survive for 5 years or more after diagnosis. With the more advanced stage 3 and 4 Hodgkin lymphoma between 59 and 90 out of every 100 people (59 to 90%) will survive for 5 years or more after diagnosis. The type of Hodgkin lymphoma will affect how successful treatment is likely to be. Younger people also tend to do better. For example, the most recent 5 year survival rates in people aged 15 to 39 were about 95%. In people aged over 80 the 5 year survival was about 30% **(Cancer Research UK. Statistics and outlook for Hodgkin lymphoma, 2014).**

Advanced Adult Soft Tissue Sarcomas

Sarcomas are a diverse group of cancerous tumours that arise mainly from the embryonic mesoderm (the mesoderm is one of the three primary layers in the very early embryo) and can be categorised as tumours arising primarily from the bone and those that arise from soft tissues. The World Health Organization has defined approximately 50 soft tissue sarcoma (STS) histologic subtypes: http://www.sciencedirect.com.ezproxy4.lib.le.ac.uk/science/article/pii/S0039610908000388_-bib1. There is overlap, however, between certain tumours and the differences between subtypes are not always distinct. Determining the exact numbers of patients diagnosed with sarcoma also is problematic, mainly because of inconsistencies in disease classification.

According to the Surveillance, Epidemiology, and End Result (SEER) database, the annual United States number of new cases of the disease of bone sarcoma and STS is approximately 15,000 cases, of which 9220 are adult STSs. As such, STS constitutes 1% of all new solid tumour cases in the United States annually with a projected number of new cases of the disease of 2.5 to 3.5 cases per 100,000 United States inhabitants per year and an overall mortality rate of 30% to 50% **(Guy Lahat *et al*, 2008).**

Furthermore, adult soft tissue sarcomas are rare tumours, with an estimated number of new cases of the disease averaging 4/100 000/year in Europe **(P.G. Casali L *et al*, 2009)**.

VI.2.2 Summary of treatment benefits

Clinical studies were not conducted for evaluating effective and safe use of Dacarbazine Lipomed 1000 mg powder for solution for infusion considering this is a generic medicine (generic medicine means a medicine that is developed to be the same as a reference medicine that has already been authorized). The available medical literature is considered sufficient to evaluate the safety and efficacy of dacarbazine in the proposed therapeutic indication(s) for Dacarbazine Lipomed 1000 mg powder for solution for infusion.

VI.2.3 Unknowns relating to treatment benefits

No special recommendation for the use of dacarbazine in the pediatric age group can be given until further data become available. Additionally, limited experience in elderly patients is available; therefore no special instructions for the use in elderly patients can be given

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	What is known	Preventability
Severe allergic reaction (hyper-sensitivity)	Patients must not be treated with Dacarbazine Lipomed in case of hypersensitivity to the active substance dacarbazine or to any of the inactive substances. Therefore, if any symptoms of a hypersensitivity reaction are	Yes. Patients and healthcare professionals are made aware that Dacarbazine Lipomed must not be used if the patients are allergic to dacarbazine or any of the other ingredients of this medicine.

Risk	What is known	Preventability
	observed, immediate termination of therapy is required. Anaphylactic reactions (severe, potentially life-threatening allergic reactions) and hypersensitivity reactions have been reported as rare adverse event, affecting 1 to 10 of 10,000 patients treated.	Anaphylactic reactions have been reported as rare adverse drug reaction, affecting 1 to 10 of 10,000 patients treated. These reactions are known as severe allergic reactions resulting in symptoms such as drop in blood pressure, swelling of the hands, feet, ankles, face, lips, mouth and throat which may cause difficulty in swallowing or breathing, rapid pulse, hives and generalised itching or skin redness). If any of these symptoms are observed, immediate termination of therapy is necessary.
Use in pregnancy	Animal studies have shown that dacarbazine may change the DNA. It must therefore be assumed that there is an increased risk of birth defects in humans. For this reason, dacarbazine must not be used during pregnancy. Additionally, handling of dacarbazine (as of all cytotoxic drugs, i.e. toxic drugs that affect living cells) should be generally avoided during pregnancy.	Yes. Dacarbazine Lipomed must not be administered if the patient is pregnant or if the patient is planning to become pregnant. The patient must take adequate contraceptive precautions during therapy. If the patient is pregnant or assumes to be pregnant or if the patient thinks of becoming pregnant, it is advised that the patient should ask the doctor for advice before treatment with Dacarbazine Lipomed.
Use in breastfeeding women	It is not known whether dacarbazine crosses the placenta or is distributed into milk. For this reason, dacarbazine must not be used whilst breast-feeding.	Yes. The patient must not breast-feed while being treated with Dacarbazine Lipomed. If the patient is breast-feeding, it is advised asking the doctor for advice treatment with Dacarbazine Lipomed.
Decreased number of white blood cells and /or	Patients with low number of white blood cells (leukopenia) and/or a low number of platelets	Yes. Patients must not be treated with Dacarbazine Lipomed if they have a low number of white

Risk	What is known	Preventability
decreased number of platelets in the blood (leukopenia and/or thrombo-cytopenia)	(thrombocytopenia) must not be treated with Dacarbazine Lipomed. The most commonly reported adverse drug reactions (affecting more than 1 in 100 and less than 1 in 10 people) of dacarbazine are blood and lymphatic system disorders which include leukopenia and thrombocytopenia. Changes in blood counts often observed (anaemia, leukopenia and thrombocytopenia) are dose-dependent and delayed, with the lowest values often only occurring after 3 to 4 weeks. In rare cases pancytopenia (deficiency of red cells, white cells, and platelets) and agranulocytosis (severely decreased number of granulocytes, a special type of white blood cells) have been described. If an overdose occurs, severe bone marrow toxicity (the decrease in production of cells responsible for providing immunity i.e. leukocytes and those responsible for normal blood clotting i.e. thrombocytes) and even bone marrow aplasia (a deficiency of all three types of blood cells [white blood cells, red blood cells and platelets]) can be expected as consequences of an overdose and the onset can be delayed by up to 2 weeks. The time to occurrence of the lowest value of leukocytes and thrombocytes can be 4 weeks. Even if an overdose is only suspected, long-term, careful monitoring through blood tests is essential.	blood cells (leukopenia) or a low number of platelets (thrombocytopenia). Like all medicines, Dacarbazine can cause side effects, although not everybody gets these side effects. Leukopenia (decreased number of white blood cells) and/or thrombocytopenia (decreased number of platelets in the blood) are known undesirable effects and are reported as commonly occuring side effects (affecting 1 to 10 of 100 patients treated). Additionally, with regards to a low number of platelets (thrombocyotopenia), the changes in blood counts are dependent on the dosage and a delayed reaction is possible, with the lowest value often occuring after 3 to 4 weeks.

Risk	What is known	Preventability
Severe liver or kidney disease	Patients with severe liver or kidney disease must not be treated with Dacarbazine Lipomed. During dacarbazine treatment, frequent monitoring of blood counts should be conducted as well as monitoring of liver (hepatic) and kidney (renal) function. If patients have mild to moderate kidney or liver insufficiency alone, treatment dose reduction is not usually required. For patients with combined kidney and liver impairment, dacarbazine elimination is prolonged. However, no confirmed recommendations on dose reductions can currently be given. If symptoms of a liver or kidney functional disorder are observed, therapy must be immediately discontinued. If veno-occlusive disease of the liver occurs (a condition in which some of the small veins in the liver are obstructed), further therapy with dacarbazine is unadvisable. A rare, uncommon complication of liver cell death (necrosis) due to a blockage or closing of the intrahepatic veins (hepatic veno-occlusive disease) has been observed after administration of dacarbazine as a monotherapy or combined chemotherapy. Symptoms included fever, eosinophilia (increased number of eosinophils, which are disease-fighting white blood cells), abdominal pain, enlarged liver, jaundice (yellow staining of the skin and the whites of the eyes),	Yes. Patients with severe liver or kidney disease must not be treated with Dacarbazine Lipomed. The doctor will monitor the liver and kidney function of the patient. During chemotherapy the patient should avoid medicines that can cause liver damage (such as; diazepam, imipramine, ketoconazole or carbamazepine). The patient should not drink alcohol. Like all medicines, this medicine can cause side effects, although not everybody gets them. The doctor will discuss this with the patient and will explain the risks and benefits of the treatment. The patient is adviced to inform their doctor immediately if they notice yellowing of the skin and eyes because of liver problems. Liver damage (hepatotoxicity) has been identified as an uncommonly occurring side effect, affecting 1 to 10 of 1000 patients treated. Additionally, a rare side effect (observed in 1 to 10 of 10,000 patients treated) called hepatic veno-occlusive disease (severe disease of the liver due to obstruction of the liver blood vessels) with hepatic necrosis (destruction of liver cells) which can be life-threatening has been identified. If this complication is suspected, the patient's doctor will consider appropriate treatment. Elevation of liver

Risk	What is known	Preventability
	skin and shock which worsened rapidly over a few hours or days. As fatal outcomes have been described, frequent monitoring of liver size, function and blood counts is particularly important during treatment. Impaired kidney function with increased blood levels of substances which have to be excreted in the urine is uncommon. It has been found that alcohol and drugs that bring about chemical liver damage are unadvisable during chemotherapy. Dacarbazine is metabolised by a specific enzyme known as cytochrome P450 enzyme, which metabolises potential toxic compounds. This must be taken into account if other medicinal products are co-administered with dacarbazine that are metabolised by the same hepatic enzymes.	enzymes as well as impaired kidney function has also been categorized as a rare side effect of Dacarbazine Lipomed.
Administration of dacarbazine and a weakened live attenuated viral vaccine for yellow fever at the same time	Treatment with Dacarbazine Lipomed must not occur at the same time when the patient receives a vaccination for yellow fever since extremely serious symptoms affecting the entire body may develop which could even lead to death.	Yes. Patients must not be treated with dacarbazine when they receive yellow fever vaccine at the same time.
Severe disease of the liver due to obstruction of the liver blood vessels (Hepatic veno-occlusive disease)	If veno-occlusive disease of the liver occurs (a condition in which some of the small veins in the liver are obstructed), therapy with dacarbazine must be stopped. A rare, uncommon complication of liver cell death (necrosis) due to a blockage or closing of the intrahepatic veins (hepatic veno-occlusive disease) has been	Yes. Like all medicines, Dacarbazine Lipomed can cause side effects, although not everybody gets them. The patient's doctor will discuss possible side effects with the patient and will explain the risks and benefits of the treatment.

Risk	What is known	Preventability
	observed after administration of dacarbazine. Symptoms included fever, eosinophilia (increased number of eosinophils, which are disease-fighting white blood cells), abdominal pain, enlarged liver, jaundice (yellow staining of the skin and the whites of the eyes), skin and shock which worsen rapidly over a few hours or days.	Hepatic veno-occlusive disease (severe disease of the liver due to obstruction of liver blood vessels) with hepatic necrosis (destruction of liver cells) which can be life-threatening is found to be a rarely occurring side effect (1 to 10 of 10,000 patients treated). If this complication is suspected, the doctor will stop treatment with Dacarbazine Lipomed.
Negative influence on the formation of blood cells (haematopoietic toxicity)	Severe haematological disturbances (affecting the blood) can occur, and therefore a very careful benefit-risk analysis must be carried out before each treatment with Dacarbazine Lipomed by the doctor. It is recommended that dacarbazine should only be administered under the supervision of a physician specialised in oncology (cancer), therefore having the facilities for regular monitoring of clinical, biochemical and haematological effects, during and after therapy. Long-term therapy can cause increased bone marrow toxicity (negative influence on the bone marrow leading to a reduction in number of blood cells, including white blood cells, red blood cells and platelets). This possible suppression of the bone marrow requires careful monitoring of the number of red and white blood cells and of platelets. The negative influence on the formation of blood cells (haematopoietic toxicity) may warrant temporary	Yes. Treatment with Dacarbazine Lipomed should only be carried out by doctors who specialise in the treatment of cancer (oncologists) or diseases of the blood (haematologists). During treatment with Dacarbazine Lipomed, frequent monitoring of the number of blood cells is required. The dose will depend on the blood cell counts and concurrent chemotherapy. The patient's doctor will calculate the dose taking into consideration the patient's body surface area, blood counts and other anticancer medicines or therapies given. Anaemia (decreased number of red blood cells), leukopenia (decreased number of white blood cells), thrombocytopenia (decreased number of platelets in the blood) and bone marrow suppression (decreased formation of all blood cells in the bone marrow) are commonly occurring side effect, affecting 1 to 10 users in 100. In addition, the changes in blood counts are dose-dependent

Risk	What is known	Preventability
	discontinuation or termination of therapy. If an overdose occurs, severe bone marrow toxicity and even bone marrow aplasia (lack of production of the three types of blood cells in the bone marrow: white blood cells, red blood cells and platelets) can be expected as consequences of an overdose and the onset can be delayed by up to 2 weeks. The time to occurrence of the lowest value of leukocytes (white blood cells) and thrombocytes (platelets) can be 4 weeks. Even if an overdose is only suspected, long-term, careful monitoring through blood tests is essential.	and delayed. The lowest values often only occur after 3 to 4 weeks. There have been reports of rarely occurring side effects (affecting 1 to 10 users in 10,000), which include pancytopenia (decreased number of all types of blood cells) and agranulocytosis (severely decreased number of granulocytes, a special type of white blood cells).
Weakening of the immune system/ increased risk of infections (Immuno-suppressant effects/ increased susceptibility to infections)	Dacarbazine is a moderate immunosuppressive agent (an agent inhibiting or preventing the activity of the immune system). Administration of live attenuated vaccines, (containing infectious agents which have been altered to become harmless or less virulent) in patients who have weakened immune systems caused by chemotherapeutic agents (including dacarbazine), may result in serious or fatal infections. Vaccination with a live attenuated vaccine should be avoided in patients receiving dacarbazine. It is recommended using an inactivated vaccine where this exists (for example for poliomyelitis, an infectious viral disease that affects the central nervous system and can cause temporary/permanent paralysis).	Yes. It is advised that prior to treatment with dacarbazine, the patient should inform the doctor about vaccination with live vaccines since dacarbazine may weaken the immune system and make the patient more likely to catch a serious infection. Therefore, the patient should not be treated with Dacarbazine Lipomed in case of vaccination with live vaccines. Like all medicines, this medicine can cause side effects, although not everybody gets them. If the patient notices signs of infection, such as sore throat and high temperature, the doctor should be informed immediately about this. Furthermore, infection has been reported as an uncommon side

Risk	What is known	Preventability
	Increased susceptibility to infections has been identified with dacarbazine treatment as an uncommonly occurring adverse event (affecting 1 to 10 patients in 100).	effect (affecting 1 to 10 of 1000 patients treated).
Administration of cyclosporin, a drug which causes the weakening of the immune system, and dacarbazine at the same time (concomitant use of cyclosporin)	If the patient is undergoing treatment with dacarbazine, the use of cyclosporin or tacrolimus should be carefully considered since use of these agents cause weakening of the immune system with the risk of lymphoproliferation (lymphoid tissue growth and reproduction).	Yes. The patient should inform the doctor, nurse or pharmacist about treatment with ccyclosporine or tacrolimus since these medicines may reduce the function of the immune system.
Administration of fotemustine (an agent used to treat metastasising melanoma), which can cause acute damage to the lungs, and dacarbazine at the same time (concomitant use of fotemustine can cause acute lung toxicity) [adult respiratory distress syndrome])	If the patient is undergoing treatment with dacarbazine, the use of fotemustine at the same time can cause acute lung toxicity (adult respiratory distress syndrome, which is a life-threatening medical condition where the lungs are unable to provide enough oxygen for the rest of the body). Fotemustine and dacarbazine should not be used alongside once another. Dacarbazine should be administered over one week after fotemustine has been administered to the patient.	Yes. The patient should inform the doctor, nurse or pharmacist about treatment with fotemustine. The patient should not be treated with dacarbazine earlier than one week after fotemustine administration to avoid damage to the lungs.
Administration of phenytoin, a drug used to treat seizures, and	If the patient is undergoing treatment with dacarbazine, the use of phenytoin should be avoided since there is an increased risk of fits (seizures), resulting from the	Yes. The patient should inform the doctor, nurse or pharmacist about treatment with phenytoin so that use of phenytoin and

Risk	What is known	Preventability
dacarbazine at the same time (concomitant use of phenytoin)	decrease of phenytoin digestive absorption.	administration of dacarbazine at the same time and thus the increased risk of fits (seizures) can be avoided. Convulsions (fits) are reported as rare side effect (affecting 1 to 10 of 10,000 patients treated).
Administration of live vaccines and dacarbazine at the same time (concomitant use of live-attenuated vaccines)	Dacarbazine is a moderate immunosuppressive agent (an agent known to inhibit or prevent the activity of the immune system). Administration of live vaccines (vaccination with an infectious agent which has been altered to become harmless or less virulent) in patients with weakened immune systems caused by chemotherapeutic agents (including dacarbazine) may result in serious infections, which could even lead to death. It is recommended using an inactivated vaccine where this exists (for example for poliomyelitis, which is an infectious viral disease that affects the central nervous system and can cause temporary/permanent paralysis).	Yes. The patients should not be vaccinated with a live vaccine (a less virulent version of the infectious agent) during treatment with dacarbazine. This is because dacarbazine may weaken the immune system and make the patient more likely to catch a serious infection.
Use of dacarbazine by patients who are treated with an oral agent to prevent the formation of blood clots (use in patients with oral anticoagulants)	In the case of cancerous diseases, anticoagulative treatment (treatment with medicines that help to prevent blot clot formation), is used more frequently due to the increased risk of blood clotting (thrombotic risk) during cancer therapy.	Yes. The patient's doctor will decide whether use of medicines to improve the blood flow should be given and will check the clotting tendency of the blood.
Injection of the solution into the	Care should be taken during the administration of the injection to	Yes.

Risk	What is known	Preventability
tissue around the vein, which can lead to tissue damage and severe pain (extravasation)	avoid extravasation (injection into the tissues around the vein), since this will cause local pain and tissue damage. If extravasation occurs, the injection should be discontinued immediately and any remaining portion of the dose should be introduced into another vein. Local disorders at the application site such as vein irritation and some of the systemic adverse reactions are thought to result from the formation of photo-degradation products. Local pain and necrosis (destruction of tissue) are to be expected following inadvertent extravasation.	Appropriate administration of dacarbazine must be paid attention to in order to prevent tissue damage and pain. Extravasation (injection of the solution into the tissue around the vein) can lead to tissue damage and severe pain. If this medicine is accidentally injected into the tissue around the vein, it will be painful and there will be tissue damage. Therefore, the solution must be administered carefully to avoid extravasation (injection of the solution into the tissue around the vein), to avoid local pain and tissue damage. If extravasation occurs the injection must be immediately interrupted and the remaining dose administered in a different vein.
Use of hepatotoxic drugs (drugs damaging liver cells) and alcohol consumption at the same time with treatment with dacarbazine (concomitant use of hepatotoxic drugs and alcohol)	The use of hepatotoxic drugs (drugs known to affect liver cells) as well as alcohol consumption must be avoided during chemotherapy in general and therefore also during treatment with dacarbazine.	Yes. The use of hepatotoxic drugs (drugs known to affect liver cells) as well as alcohol consumption must be avoided during chemotherapy.

Important potential risks:
Not applicable

Missing information:

Risk	What is known
Use in children	Dacarbazine is not recommended for use in children until further data become available.
Use in elderly	Limited experience in elderly patients is available; therefore no special instructions for the use in elderly patients can be given.

VI.2.5 Summary of risk minimisation measures by safety concern

The Summary of Product Characteristics (SPC) of Dacarbazine Lipomed 1000 mg powder for solution for infusion 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). All relevant risk minimization measures are described in the SPC and PL of Dacarbazine Lipomed 1000 mg powder for solution for infusion.

No additional risk minimization measures are proposed for this generic medicine.

VI.2.6 Planned post authorisation development plan

No post authorisation studies are planned for this product.

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

This section is not applicable as this is version 01 of the RMP.