VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Epithelial ovarian cancer:

Ovarian cancer forms in tissues of the ovary (woman reproductive gland in which the eggs are formed).[1] Epithelial ovarian cancer (cancer develops from the cells that surround the outside of ovary) is second most common type of ovarian cancer having 25 cases out of 100 cases of ovarian cancer. Fifty out of 100 cases of epithelial ovarian cancer are seen in women aged 75 years or above.[2] Ovarian cancer is the sixth most common cancer in UK, with around 7,400 cases in 2014. Between 2012 and 2014, more than half of ovarian cancer cases in the UK were identified in women aged 65 and over.[3] In females in the UK, ovarian cancer is the fifth most common cause of death due to cancer,, with around 4,100 deaths in 2014. In Europe, around 42,700 women died from ovarian cancer in 2012. Worldwide, around 152,000 women died from ovarian cancer in 2012.[4]

VI.2.2 Summary of treatment benefits

Epithelial ovarian cancer:

A study including 80 patients with advanced ovarian cancer, received treosulfan treatment. After the treosulfan treatment 15 patients had increased their life span about 41 months, 27 patients had increased their life span about 18 months and had stable disease in which the cancer did not increase or decrease in extent and severity. Remaining 38 patients' life span was increased about 5 months after the treosulfan treatment.

VI.2.3 Unknowns relating to treatment benefits

The effectiveness of treosulfan in children has not been established. Additionally, there are no data available regarding use of treosulfan in pregnant and breast-feeding woman and its effect on ability to reproduce (fertility).

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions	Allergic reactions (e.g. itching, rash, swelling of the face, lips, tongue and/or throat with difficulties in swallowing or breathing, drop of blood pressure) are rare (may affect up to 1 in 1,000 treated people) side effects reported with treosulfan use.	Treosulfan should not be used in patients allergic to treosulfan. Patients should tell their doctor or nurse immediately if they notice any of the allergic reactions like itching, rash, swelling of the face, lips, tongue and/or throat with difficulties in swallowing or breathing, drop in blood pressure.
Decrease in the number of blood cells leading to infections	Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer	Treosulfan should not be used in patients who do not have enough

Risk	What is known	Preventability
(myelosuppression leading to infections)	red blood cells, white blood cells, and platelets, which in turn increases the risk of infections. The risk of developing certain types of infection is increased while on treosulfan treatment. Reduction in white blood cells (which makes infections more likely), platelets (which may cause bleeding from gums, mouth or nose and may cause unexpected bruising) or red blood cells (which can make the skin pale and cause weakness or breathlessness) are very common (may affect more than 1 in 10 treated people), infections caused by fungi, viruses or bacteria are common (may affect up to 1 in 10 treated people) and severe general infection (sepsis) is a very rare (may affect up to 1 in 10,000 treated people) side effects reported with treosulfan use.	blood cells (severe bone marrow depression). Patients should talk to their treating doctor or nurse, before using treosulfan, if they experience reduction in blood cells as this may become worse with ongoing treatment. Blood tests will be performed at shorter intervals starting with the third course of treatment. It is especially important when combined with other forms of therapy that supresses the bone marrow function such as radiotherapy (treatment of diseases such as cancer by using radiation). Patients should tell their doctor or nurse immediately if they notice any of the following: • Fever or infection: if patients have a body temperature of 38 °C or higher, experience sweating or notice any other signs of infection (since they might have fewer white blood cells than normal). • Weakness, becoming short of breath, or if their skin turns pale (since they might have fewer red blood cells than normal). • Bleedings from gums, mouth or nose, or if unexpected bruising (since they might have fewer platelets than normal). Before each administration, patient should have blood tests to check the number of blood cells before receiving Treosulfan 5g powder for solution for infusion. Blood tests should be performed at shorter intervals starting with the third course of treatment.

Risk	What is known	Preventability
Secondary malignancy	A secondary malignancy is a new cancer that occurs in an individual as a result of previous treatment with radiation or chemotherapy (treatment of disease by the use of chemical substances). Different types of blood cancer (after long-term treatment) is an uncommon (may affect up to 1 in 100 treated people) side effect reported with treosulfan use.	Patients should be aware of different types of blood cancer that may occur after long-term treatment with treosulfan.

Important potential risks

Risk	What is known
A heart muscle disease (cardiomyopathy)	Cardiomyopathy is a long term disease of the heart muscle (myocardium), in which the muscle is abnormally enlarged, thickened, and/or stiffened. The weakened heart muscle loses the ability to pump blood effectively, resulting in irregular heartbeats and possibly even heart failure. Cardiomyopathy is a very rare (may affect up to 1 in 10,000 treated people) side effect reported with treosulfan use. Patients should talk to their doctor or pharmacist, if they develop cardiomyopathy.
Harmful effects to the lungs (pulmonary toxicity)	Difficulty in breathing (inflammation, scarring or infection of the lungs) is a very rare (may affect up to 1 in 10,000 treated people) side effect reported with treosulfan use. Patients should talk to their doctor or nurse before using treosulfan, if they develop swelling of the lungs which causes shortness of breath (allergic alveolitis or pulmonary fibrosis) and treatment with treosulfan should be stopped.
Swelling of the urinary bladder causing pain or more frequent urgent urination, with or without presence of bloody urine (haemorrhagic cystitis)	Swelling of the urinary bladder (hollow organ in the lower abdomen that stores urine) causing pain or more frequent urgent urination, with or without bloody urine (haemorrhagic cystitis) is a very rare (may affect up to 1 in 10,000 treated people) side effect reported with treosulfan use. Patients are advised to drink more fluids than usual for up to 24 hours after treosulfan treatment because of the possible development of haemorrhagic cystitis.

Risk	What is known
Increased risk of generalised infection with live vaccines	Treatment with anticancer medicines may increase the risk of generalised infection after some vaccinations. Therefore, patient should not receive vaccination with live vaccines.
Painful redness or swelling at the injection site due to leakage (local painful inflammatory reactions due to extravasation)	Extravasation is leakage of medicine, from a blood vessel or tube into the tissue around it. When treosulfan is not carefully administered into a blood vessel, painful swelling of the surrounding tissues may occur. Painful redness or swelling at the injection site (in the case of treosulfan solution leakage into the surrounding tissue) is a very rare (may affect up to 1 in 10,000 treated people) side effect reported with treosulfan use. Patients should immediately tell to their doctor or pharmacist if they experience pain, redness or swelling at the site of injection.

Missing information

Risk	What is known
Use during pregnancy and breastfeeding (use during pregnancy and lactation).	No data are available on the use of treosulfan in pregnant women and it is unknown if treosulfan is passes into breast milk. Patient should not use treosulfan if she is pregnant or breastfeeding unless her doctor considers it as absolutely necessary. Patient must also use effective contraception (pregnancy prevention measure) during treatment, e.g. birth control pill and for the first six months after treatment. If patient is pregnant or breast-feeding, thinks she may be pregnant or is planning to have a baby, she should ask doctor for advice before taking this medicine.
Effect on ability to reproduce (effect on fertility)	No information is available regarding effect of treosulfan on ability to reproduce.
Use in children (use in paediatric population)	The safety and effectiveness of treosulfan in children has not been established. Hence, treosulfan is not advised for use in children.

VI.2.5 Summary of 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.

The Summary of Product Characteristics and the Package leaflet for Treosulfan can be found in the Treosulfan EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post-authorisation development plan

There is no planned post-authorisation development plan for Treosulfan 5 g powder for solution for infusion.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Version 1.0	20 Feb 2017	**Important Identified Risks** • Allergic reactions • Myelosuppression leading to infections • Secondary malignancy **Important Potential Risks** • Cardiomyopathy • Pulmonary toxicity • Haemorrhagic cystitis • Increased risk of generalised infection with live vaccines • Local painful inflammatory reactions due to extravasation **Missing information** • Use during pregnancy and lactation • Effect on fertility • Use in paediatric population	Initial version
Version 1.1	31 Mar 2017	No change in the safety concerns	The RMP was revised as per the validation issue received from Germany. Hence, product name/pharmaceutical form has been changed in line with the reference product in Germany.

Version	Date	Safety Concerns	Comment
Version 1.2	28 Jul 2017	No change in the safety concerns	The RMP was revised as per Day 70 comments from RMS (UK) and updated SPC and PIL accordingly.
Version 1.3	31 Oct 2017	No change in the safety concerns	The RMP has been updated as per Day 120 and Day 145 comments received from RMS and CMSs and updated SPC and PIL accordingly.