Part VI: Summary of the risk management plan

Summary of risk management plan for Busulfan

This is a summary of the risk management plan (RMP) for Busulfan Kabi. The RMP details important risks of Busulfan Kabi, how these risks can be minimised, and how more information will be obtained about Busulfan Kabi risks and uncertainties (missing information).

Busulfan Kabi SmPC and its PL give essential information to healthcare professionals and patients on how Busulfan Kabi should be used.

I. The medicine and what it is used for

Busulfan Kabi is authorised for –

Busulfan followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option.

Busulfan following fludarabine (FB) is indicated as conditioning treatment prior to haematopoietic progenitor cell transplantation (HPCT) in adult patients who are candidates for a reduced-intensity conditioning (RIC) regimen.

Busulfan followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients.

It contains busulfan as the active substance.

Further information about the evaluation of Busulfan Fresenius Kabi benefits can be found in Busilvex EPAR, including in its plain-language summary, available on the EMA website, under the medicine's.

https://www.ema.europa.eu/en/medicines/human/EPAR/busilvex

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Busulfan Kabi, together with measures to minimise such risks and the proposed studies for learning more about Busulfan Kabi risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Busulfan Kabi is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Busulfan Kabi are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Busulfan Kabi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	– Myelosuppression – Hepatic veno-occlusive disease – Drug interaction with paracetamol – Interstitial pulmonary fibrosis – Seizure – Reproductive toxicity – Impaired fertility – Lens disorders/cataract – Secondary malignancies
Important potential risks	– Cardiac tamponade – Drug interaction with itraconazole – Medication error
Missing information	– Use in the elderly – Use in obese children and adolescents – Use in patients with renal impairment – Use in patients with hepatic impairment – Use during lactation

II.B Summary of important risks

Important identified risk - Myelosuppression	
Evidence for linking the risk to the medicine	Reports of myelosuppression from busulfan derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	In patients with impaired bone marrow function and other cytotoxic treatments
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL Section 2, What you need to know before you use Busulfan Fresenius Kabi" Routine risk minimisation activities recommending specific clinical measures to address the risk: Frequent complete blood counts, including differential white blood cell counts, and platelet counts should be monitored during the treatment and until recovery is achieved. Additional risk minimisation measures Not applicable

Important identified risk - Hepatic veno-occlusive disease	
Evidence for linking the risk to the medicine	Reports of hepatic veno-occlusive disease from busulfan derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients who have received prior radiation therapy and greater than or equal to three cycles of chemotherapy, or prior progenitor cell transplant
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" and 4.5 "Interaction with other medicinal products and other forms of interaction" and Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you use Busulfan Fresenius Kabi" and section 4 "Possible side effects"

	Routine risk minimisation activities recommending specific clinical measures to address the risk: By monitoring early symptoms and regular checking liver enzymes levels. Patients should tell their doctor immediately if they experience weight gain, increase in abdominal circumference, pain in right upper quadrant of the abdomen etc. Additional risk minimisation measures Not applicable

Important identified risk - Drug interaction with paracetamol	
Evidence for linking the risk to the medicine	Reports of drug interaction with paracetamol from busulfan derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients under treatment of paracetamol with busulfan.
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" and in SmPC section 4.5 "Interaction with other medicinal products and other forms of interaction". Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before use Busulfan Fresenius Kabi ". Routine risk minimisation activities recommending specific clinical measures to address the risk: Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with busulfan due to a possible decrease in the metabolism of busulfan Additional risk minimisation measures Not applicable

Important identified risk - Interstitial pulmonary fibrosis	
Evidence for linking the risk to the medicine	Reports of interstitial pulmonary fibrosis from busulfan derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	The patients with prior history of mediastinal or pulmonary radiation.

Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you use BusulfanFresenius Kabi" Routine risk minimisation activities recommending specific clinical measures to address the risk. Attention should be paid to this pulmonary issue in patients with prior history of mediastinal or pulmonary radiation. Additional risk minimisation measures Not applicable

Important identified risk - Seizure	
Evidence for linking the risk to the medicine	Reports of seizure from busulfan derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patient under treatment with high dose of busulfan treatment, history of seizures. Adults and children using concomitant administration of either phenytoin or benzodiazepines.
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.2 "Posology and method of administration", 4.4 "Special warnings and precautions for use" and 4.5 "Interaction with other medicinal products and other forms of interaction" Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you use Busulfan", and section 4 "Possible side effects" Routine risk minimisation activities recommending specific clinical measures to address the risk: It is recommended to administer anticonvulsants 12 h prior to busulfan to 24 h after the last dose of busulfan. Special caution should be exercised when administering the recommended dose of busulfan to patients with a history of seizures. Additional risk minimisation measures Not applicable

Important identified risk - Reproductive toxicity	
Evidence for linking the risk to the medicine	Reports of reproductive toxicity from busufan derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients who are pregnant or breastfeeding, think they may be pregnant or are planning to have a baby, should ask their doctor before receiving busulfan therapy. Women must not be pregnant during treatment with busulfan and for up to 6 months after treatment. Adequate contraceptive precautions should be used when either partner is receiving busulfan therapy.
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.6 "Fertility, pregnancy and lactation" Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you use Busulfan" and section 4 "Possible side effects" Routine risk minimisation activities recommending specific clinical measures to address the risk: Patients who are pregnant or breastfeeding, think they may be pregnant or are planning to have a baby, should ask their doctor before receiving busulfan therapy. Women must not be pregnant during treatment with busulfan and for up to 6 months after treatment. Adequate contraceptive precautions should be used when either partner is receiving busulfan therapy. Additional risk minimisation measures Not applicable

Important identified risk - Impaired fertility	
Evidence for linking the risk to the medicine	Reports of impaired fertility of busulfan derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Men and Women of childbearing potential
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.6 "Fertility, pregnancy and lactation" Listed in SmPC section 4.8 "Undesirable effects":

	Guidance in PL section 2 "What you need to know before you use Busulfan" and section 4 "Possible side effects" Routine risk minimisation activities recommending specific clinical measures to address the risk: It is advised not to father child during the treatment and up to 6 months after treatment and to seek advice on cryo conservation of sperm prior to treatment because of the possibility of irreversible infertility. Additional risk minimisation measures Not applicable

Important identified risk - Lens disorders/cataract	
Evidence for linking the risk to the medicine	Reports of Lens disorders/cataract from busulfan derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with underlying lens disorders
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you use Busulfan" and section 4 "Possible side effects" Routine risk minimisation activities recommending specific clinical measures to address the risk: By monitoring of early symptoms. Patients should inform their doctor immediately if they experience blurred vision or clouding of the lens of the eye or they have prior history of any eye disorders. Additional risk minimisation measures Not applicable

Important identified risk - Secondary malignancies	
Evidence for linking the risk to the medicine	Reports of secondary malignancies of busulfan derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with Leukaemia disorders

Risk minimisation measures	Routine risk minimisation measures Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you use Busulfan" Routine risk minimisation activities recommending specific clinical measures to address the risk: Before starting therapy with busulfan, patients should tell their doctor if they have liver, kidney, heart or lung problems. Additional risk minimisation measures Not applicable

Important potential risk - Cardiac tamponade	
Evidence for linking the risk to the medicine	Reports of cardiac tamponade of busulfan derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with underlying cardiac function disorders and undergoing bone-marrow transplantation.
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use", Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you use Busulfan" Routine risk minimisation activities recommending specific clinical measures to address the risk: Cardiac function should be monitored regularly in patients receiving busulfan Additional risk minimisation measures Not applicable

Important potential risk - Drug interaction with itraconazole	
Evidence for linking the risk to the medicine	Reports of drug interaction with itraconazole of busulfan derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients under concurrent treatment with busulfan and itraconazole.

Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" and in SmPC section 4.5 "Interaction with other medicinal products and other forms of interaction". Guidance in PL section 2 "What you need to know before you use Busulfan" and section 4 "Possible side effects" Routine risk minimisation activities recommending specific clinical measures to address the risk: Patients who are concurrently treated with busulfan and itraconazole should be closely monitored for signs of busulfan toxicity. Additional risk minimisation measures Not applicable

Important potential risk - Medication/dispensing errors	
Evidence for linking the risk to the medicine	Reports of medication/dispensing errors of busulfan derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Incorrect method of administration or dispensing of product
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.2 "Posology and method of administration" and section 4.4 "Special warnings and precautions for use", Guidance in PL section 2 "What you need to know before you use Busulfan Fresenius Kabi " and section 3 "How to use Busulfan Fresenius Kabi" Routine risk minimisation activities recommending specific clinical measures to address the risk: Dosing and administration of busufan should be in accordance with guidance available in product label. Busulfan Fresenius Kabi will be administered by a health care professional experienced in the use of cytotoxic medicines. Additional risk minimisation measures Not applicable

Missing information: Use in the elderly	
Risk minimisation measures	Routine risk minimisation measures

	Guidance in SmPC section 4.2 "Posology and method of administration" and section 4.4 "Special warnings and precautions for use" Guidance in PL section 2 "How to use Busulfan Fresenius Kabi " Routine risk minimisation activities recommending specific clinical measures to address the risk: Due to the limited information, dose adjustment is not recommended in patients over 60 years of age, but the treating doctor might adjust the dose of busulfan therapy according to the patient's age. Additional risk minimisation measures Not applicable

Missing information: Use in obese children and adolescents	
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.2 "Posology and method of administration" and section 4.4 "Special warnings and precautions for use" Guidance in PL section 2 "How to use Busulfan Fresenius Kabi " Routine risk minimisation activities recommending specific clinical measures to address the risk: The medicinal product is not recommended in obese children and adolescents with body mass index Weight (kg)/ (m2) > 30 kg/m² until further data become available. Additional risk minimisation measures Not applicable

Missing information: Use in patients with renal impairment	
Risk minimisation measures	Guidance in SmPC section 4.2 "Posology and method of administration" and section 4.4 "Special warnings and precautions for use" Guidance in PL section 2 "How to use Busulfan Fresenius Kabi " Routine risk minimisation activities recommending specific clinical measures to address the risk: There is limited information available regarding the use of busulfan in patients with kidney impairment, as studies have not been conducted in this group of patients. As busulfan is only moderately excreted in the urine, dose

	modification is not recommended in these patients. However, caution is recommended. Other routine risk minimisation measures beyond the Product Information: None Legal status: Restricted medical prescription.

Missing information: Use in patients with hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.2 "Posology and method of administration" and section 4.4 "Special warnings and precautions for use" Guidance in PL section 2 "How to use Busulfan Fresenius Kabi " Routine risk minimisation activities recommending specific clinical measures to address the risk: Busulfan has not been studied in patients with liver impairment so there is limited information available regarding the use of busulfan in these patients. Since busulfan is mainly metabolised through the liver, caution should be exercised when busulfan is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment. It is recommended when treating these patients that liver parameters should be monitored regularly for 28 days following transplant for early detection of liver problems. Additional risk minimisation measures Not applicable

Missing information: Use during lactation	
	Routine risk minimisation measures Guidance in SmPC section 4.6 "Fertility, pregnancy and lactation" and section 4.4 "Special warnings and precautions for use" Guidance in PL section 4 "Possible side effects " Routine risk minimisation activities recommending specific clinical measures to address the risk: It is unknown whether busulfan and DMA are excreted in human milk. Because of the potential for tumorigenicity shown for busulfan in human and animal studies, breast

	feeding should be discontinued during treatment with busulfan. Additional risk minimisation measures Not applicable

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Busulfan Kabi.

II.C.2 Other studies in post-authorisation development plan

There are no on-going or closed studies for Busulfan Kabi**.**