Summary of the Risk Management Plan (RMP) for Mirasol System for Platelets

(Mirasol-treated Platelets)

Version 1.0 (October 2020)

Based on part VI EU RMP Revision 2 (August 2018)

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of the Mirasol System (Mirasol-treated platelets) is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of the Mirasol System (Mirasol-treated platelets) in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Terumo Blood and Cell Technologies is fully responsible for the accuracy and correctness of the content of the published summary RMP of the Mirasol System (Mirasol-treated platelets).

1 The Medicine and What it is Used for

Mirasol-treated platelets are used for transfusion to patients who experience blood loss or who are not able to produce platelets due to suppressed hematopoiesis, just as untreated platelets are used. Platelet transfusion is well-established in medical practice.

Mirasol treatment offers a broad approach to pathogen reduction in platelets for transfusion by inactivating a wide range of clinically-relevant viruses, bacteria, and parasites as well as donor leukocytes. Used in addition to currently-approved donor and blood screening practices, it provides an additional clinical safety benefit to patients, particularly immunocompromised patients or those who need chronic transfusion support

1.1 Summary of Treatment Benefits

The Mirasol System results in a transfusable blood product that has been pathogen reduced. Mirasol-treated platelets decrease the likelihood of transfusion-transmitted infections from unscreened and undetected pathogens. Mirasol treatment provides white blood cell inactivation, which may decrease the likelihood of adverse events such as transfusion-associated graft-versus-host disease, febrile non-hemolytic transfusion reactions, alloimmunization, and transfusion-related immunomodulation (TRIM) associated with residual white blood cells.

2 Summary of Safety Concerns

Important risks of Mirasol-treated Platelets, together with measures to minimise such risks and the proposed studies for learning more about Mirasol-treated Platelet's risks, are outlined below.

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

- Engineering controls assuring that the treatment process is performed correctly
- Specific information, such as warnings, precautions, and advice on correct use, in the product labeling.
- The national requirements for effective transfusion of pathogen reduced platelets (e.g. platelet dose, leukoreduction,etc.) and the associated quality assurance.
- 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 periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

2.1 List of Important Risks and Missing Information

Important risks of Mirasol-treated platelets 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

Mirasol-treated platelets 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);

Important Identified Risks	Lower corrected count increments (CCIs)
	A potential increase in platelet utilization
Important Potential Risks	Ineffective and delayed therapy resulting in severe anemia or bleeding.
	Sepsis secondary to transfusion-transmitted infection
	Transfusion-transmitted cytomegalovirus
Missing Information	Use during pregnancy and breastfeeding
	Use in patients under 18 years of age

2.3 Summary of Important Identified Risks

Important identified risk: Lower corrected count increments (CCIs)	
Evidence for linking the risk to the medicine	Clinical and hemovigilance studies have shown that the performance of pathogen-reduced platelets is decreased compared to conventional platelets, as measured by surrogate endpoints (i.e. CCI, Recovery and Survival values). Although CCI may be lower in patients receiving Mirasol-treated platelets, there are no statistically significant increases in bleeding complications after transfusion of Mirasol-treated platelets. Mirasol-treated platelets meet criteria for transfusion and maintain good quality per national requirements throughout storage for up to 5 days in plasma and for up to 7 days in platelet additive solution (PAS).
Risk factors and risk groups	People with hematological or oncological disorders who are thrombocytopenic due to their disease or its treatment.
Risk minimisation measures	Routine risk minimisation measures: • Disclosure of residual risk • Management of platelet transfusion per established medical practice Additional risk minimisation measures: • None

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • MIPLATE study CCIs will be determined as part of a secondary outcome measure in the post-authorization efficacy study. See Section 3 of this summary for an overview of the study objectives.
Important identified risk: A potential increase in platelet utilization	
Evidence for linking the risk to the medicine	Multiple studies have shown that the performance of pathogen-reduced platelets is decreased compared to conventional platelets, as measured by surrogate endpoints (i.e. CCI, Recovery and Survival values). These data suggest the possibility that the study population receiving Mirasol treated platelets may be at risk of requiring a slightly higher dose of platelets compared to those receiving conventional platelets. No change in clinically-relevant endpoints (e.g. bleeding) has been seen with Mirasol-treated platelets to date. Cochrane reviewers[1] found 1) high-quality evidence that pathogen-reduced platelet transfusions increase the risk of platelet refractoriness and the platelet transfusion requirement, and 2) moderate-quality evidence that pathogen-reduced platelet transfusions do not affect all-cause mortality, the risk of clinically significant or severe bleeding, or the risk of a serious adverse event. These data were consistent findings for each PRT system for platelets.
Risk factors and risk groups	People with hematological or oncological disorders who are thrombocytopenic due to their disease or its treatment.
Risk minimisation measures	Routine risk minimisation measures: • Disclosure of residual risk • Management of platelet transfusion per established medical practice Additional risk minimisation measures: • None

[1] Estecourt LJ, Malouf R, Hopewell S, Trivella M, Doree C, Stanworth SJ, Murphy MF. Pathogen-reduced platelets for the prevention of bleeding (Review). Cochrane Database of Systematic Reviews 2017;7

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • MIPLATE study Platelet refractoriness will be evaluated as a secondary outcome measure in the post-authorization efficacy study. See section 3 of this summary for an overview of the study objectives.

2.4 Summary of Important Potential Risks

Important Potential Risk: Ineffective and delayed therapy resulting in severe anemia or bleeding This risk can potentially occur due to any errors leading to over-illumination or high product temperatures during the Mirasol treatment process resulting in a transfused product that does not provide the expected therapeutic benefit.	
Risk minimisation measures	Routine risk minimisation measures: • Equipment design • Software controls • Temperature management system • Training and labelling; clear IFU, Operator's Manual, training describing correct processing techniques. Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • MIPLATE study The primary outcome measure for the post-authorization efficacy study is a bleeding parameter. See Section 3 of this summary for an overview of the study objectives.
Important Potential Risk: Sepsis secondary to transfusion-transmitted infection This risk can potentially occur if the transfused product contains residual, active bacteria as a result of possible pathogen resistance, high pathogen load, or under-illumination. No known and currently-available pathogen reduction process has been shown to successfully eliminate all potential bloodborne pathogens, nor do routine donor screening and testing practices entirely eliminate the risk of transfusion-transmitted infections in conventional platelets.	

Risk minimisation measures	Routine risk minimisation measures: • Training and labelling; clear IFU, Operator's Manual, training describing correct processing techniques. Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • MIPLATE study The occurrence of bacterial sepsis will be captured as a safety endpoint in the post-authorization efficacy study. See Section 3 of this summary for an overview of the post-authorisation development plan.
Important Potential Risk: Transfusion-transmitted cytomegalovirus This risk can potentially occur as a result of ineffective leukoreduction or under-illumination.	
Risk minimisation measures	Routine risk minimisation measures: • Training and labelling; clear IFU, Operator's Manual, training describing correct processing techniques. Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

2.5 Summary of Important Missing Information

Important Missing information: Use during pregnancy and breastfeeding	
Risk minimisation measures	Routine risk minimisation measures: • Product labeling includes a warning about phthalates (DEHP) Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Important Missing information: Use in patients under 18 years of age	
Risk minimisation measures	Routine risk minimisation measures: • Product labeling includes a warning about phthalates (DEHP) Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • MIPLATE study Subjects under 18 years of age are eligible for enrolment in the post-authorization efficacy study. See Section 3 of this summary for an overview of the post-authorisation development plan.

3 Post-Authorization Development Plan

3.1 Studies which are Conditions of the Marketing Authorization

The following study is a condition of the marketing authorisation: MIPLATE study (post-authorization efficacy study)

Study/Activity	Objectives	Status
Efficacy of Mirasol-treated Apheresis Platelets in Patients with Hypoproliferative Thrombocytopenia (MIPLATE) NCT02964325	A prospective, multi-center, controlled, randomized, non-inferiority study to evaluate the clinical effectiveness of Conventional versus Mirasol-treated apheresis platelets in subjects with hypoproliferative thrombocytopenia who are expected to have platelet count(s) $\leq 10{,}000/\mu L$ requiring ≥ 2 platelet transfusions.	Terminated (actual enrollment 330 subjects). Final study report to be submitted Q1/Q2 2021.

3.2 Other Studies in Post-Authorization Development Plan

Study/Activity	Objectives	Status
None	N/A	N/A

4 Summary of Changes to the Risk Management Plan

Not Applicable.