SUMMARY OF RISK MANAGEMENT PLAN

for

NORMOSANG®

(human hemin)

Active substance:	Human hemin
Product(s) concerned (brand name(s)):	Normosang
MAH / Applicant name:	Recordati AG
Document status:	Final
Date of final sign off of the RMP Public Summary:	07 July 2025
Version number of RMP when this module was last updated:	2.1

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 "Normosang" 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 "Normosang" in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. "Recordati AG" is fully responsible for the accuracy and correctness of the content of the published summary RMP of "Normosang".

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Summary of the risk management plan for Normosang®

This summary of risk management plan is prepared in alignment with the current European Risk Management Plan (RMP) for Normosang (version 2.1, dated 20 Dec. 2021).

The RMP details important risks of Normosang, how these risks can be minimized, and how more information will be obtained about Normosang's risks and uncertainties (missing information).

Normosang's summary of product characteristics and its package leaflet give essential information to healthcare professionals and patients on how Normosang should be used.

This summary of the RMP for Normosang should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary.

Important new concerns or changes to the current ones will be included in updates of Normosang's RMP.

I. The Medicine and What it is Used for

Normosang is authorised for the treatment of acute attacks of hepatic porphyria (acute intermittent porphyria, variegate porphyria and hereditary coproporphyria).

It contains human hemin as the active substance, and it is given intravenously (IV).

II. Risks associated with the Medicine and Activities to Minimise or further characterise the risks

Important risks of Normosang, together with measures to minimise such risks and the proposed studies for learning more about Normosang's 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 the case of Normosang, these measures are supplemented with additional risk minimisation measures (aRMMs) mentioned below under the relevant important risks, outlined in the next sections.

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.

1. List of important risks and missing information

Important risks of Normosang are risks that need special risk management activities to further investigate or minimize 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 Normosang. 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 (eg, on the long-term use of the medicine).

Important identified risks	• Thrombosis • Extravasation • Injection site necrosis
Important potential risks	• None
Missing information	• None

2. Summary of important risks

Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Thrombosis

Important identified risk of thrombosis	
Evidence for linking the risk to the medicine	Normosang has been reported to increase serum ferritin [SmPC for Normosang]. Iron is a pro-oxidant cofactor associated with an increased production of hydroxyl radicals in cardiovascular tissues and increased progression of atherosclerosis. In experimental models, a moderate iron overload markedly accelerated thrombus formation, impaired vasoreactivity, and enhanced the production of reactive oxygen species [Franchini et al, 2008]. Injection site thrombosis and venous thrombosis are listed in the SmPC for Normosang. Section 4.4 of the SmPC states peripheral venous alterations have been reported after repeated infusions and that the risk of thrombosis at the caval vessels cannot be excluded. **Post-marketing experience and literature.** Cumulatively, a total of 68 case reports describing 79 events (55 serious, 24 non-serious) pertaining to thrombosis were identified from post-marketing experience. Injection site thrombosis and venous thrombosis are listed in the SmPC for Normosang. Also, Section 4.4 of the SmPC states that the risk of thrombosis at the caval vessels cannot be excluded.
Risk factors and risk groups	Repeated infusions of Normosang in the same location may lead to venous thrombosis. In case reports identified from post-marketing experience, event onset occurred after years of Normosang treatment.
Risk minimisation measures	<u>Routine risk minimisation measures</u> Section 4.4 of the SmPC advises that the infusion should be administered over at least 30 minutes in a large vein of the forearm or in a central vein to prevent vein irritation. Section 4.4 of the SmPC also recommends rinsing the vein with 100ml of 0.9% sodium chloride after the infusion as peripheral venous alterations have been reported after repeated infusions and can prevent the use of the affected veins for further infusions, necessitating the use of a central venous line. Legal status: Medicinal product subject to medical prescription <u>Additional risk minimisation measures</u> Healthcare Professional Guide: this guide is provided to all healthcare professionals involved in the prescribing/administration of Normosang to provide them with information on the risks associated with Normosang administration, including thrombosis, extravasation and necrosis, and the precautions to take in order to reduce them. Although it is recognised that extravasation, thrombosis and necrosis are conditions associated with the IV administration of medications, their risk must be proactively managed with the aim of preventing an incident.

IV = Intravenous; SmPC = Summary of Product Characteristics

Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Extravasation

Important identified risk of extravasation	
Evidence for linking the risk to the medicine	Peripheral venous alterations have been reported after repeated infusions. In addition, if the IV cannula is in place for too long, due to mechanical irritation and irritation due to the injection fluid, vascular damage may occur, which may lead to extravasation; in cases of extravasation, skin discoloration may also occur. **Post-marketing experience and literature.** Cumulatively, a total of 70 case reports describing 110 events (20 serious, 90 non-serious) pertaining to extravasation were identified from post-marketing experience. Extravasation is listed in the SmPC for Normosang.
Risk factors and risk groups	The risk of extravasation is increased in: • Cannulation in the antecubital fossa or over joint spaces • Elderly patients due to: o Interference with the cannula when the patient is confused or agitated o Reduced pain sensation o Fragile skin and veins • Unconscious, sedated, or confused patients • Patients suffering from decreased sensation or circulation • Inadequate securing of the cannula • Inadequate visibility of the cannula and surrounding tissue • Central venous access device use; diagnosis of extravasation can be delayed, therefore extra vigilance is required Porphyria patients may have additional risk of extravasation due to: • Fragile, mobile veins that are difficult to cannulate • Repeated venepunctures or cannula sites from previous treatments
Risk minimisation measures	<u>Routine risk minimisation measures</u> Section 2 of the PL notes that in order to diminish the risk of extravasation, the nurse/doctor will test the cannula before the infusion and will check it regularly during the infusion. Section 4.4 also of the SmPC also advises to test the cannula before infusing Normosang and check it regularly during the infusion. In addition, Section 4.4 advises that as the diluted solution is hypertonic, it should be administered by very slow IV infusion only. To prevent vein irritation, the infusion should be administered over at least 30 minutes in a large vein of the forearm or in a central vein. It is recommended to rinse the vein with 100 ml of 0.9% sodium chloride after the infusion as peripheral venous alterations have been reported after repeated infusions and can prevent the use of the affected veins for further infusions, necessitating the use of a central venous line. Legal status: Medicinal product subject to medical prescription.

	Additional risk minimisation measures Healthcare Professional Guide: this guide is provided to all healthcare professionals involved in the prescribing/administration of Normosang to provide them with information on the risks associated with Normosang to provide them with information on the risks associated to Normosang administration, including thrombosis, extravasation and necrosis, and the precautions to take in order to reduce them. Although it is recognised that extravasation, thrombosis and necrosis are conditions associated with the IV administration of medications, their risk must be proactively managed with the aim of preventing an incident

IV = Intravenous; PL = Package Leaflet; SmPC = Summary of Product Characteristics

Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Injection site necrosis

Important identified risk of injection site necrosis	
Evidence for linking the risk to the medicine	The significance of the necrosis may be negligible when few injections are given, but if multiple injections are given, especially in the same area over a protracted period of time, the areas of necrosis may become quite large and result in large areas of fibrosis of the tissues. This may be manifested by hard nodules deep in the tissues and even sunken areas of scar tissue seen on the surface of the skin. Dystrophic calcification of the scar tissue can occur with time resulting in even more painful areas. Once this occurs, operative excision of the area is the only therapy **Post-marketing experience and literature.** Cumulatively, a total of 2 case reports describing 2 events (1 serious, 1 non-serious) of Injection site necrosis were identified from post-marketing experience. Injection site necrosis is listed in the SmPC for Normosang
Risk factors and risk groups	Repeated infusions of Normosang in the same location may lead to Injection site necrosis. In case reports identified from post-marketing experience, event onset occurred after years of Normosang treatment.
Risk minimisation measures	Routine risk minimisation measures Legal status: Medicinal product subject to medical prescription. Additional risk minimisation measures Healthcare Professional Guide: this guide is provided to all healthcare professionals involved in the prescribing/administration of Normosang to provide them with information on the risks associated with Normosang to provide them with information on the risks associated to Normosang administration, including thrombosis, extravasation and necrosis, and the precautions to take in order to reduce them. Although it is recognised that extravasation, thrombosis and necrosis are conditions associated with the IV administration of medications, their risk must be proactively managed with the aim of preventing an incident.

IV = Intravenous; SmPC = Summary of Product Characteristics

3. Table of ongoing and planned studies in the Post-Authorisation Pharmacovigilance Development Plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 – Required additional pharmacovigilance activities				
None.				

4. Summary of Post Authorisation efficacy development plan

There are no post-authorisation efficacy studies planned or ongoing for Normosang.