Summary of risk management plan for Xromi 100 mg/mL Oral Solution (Hydroxycarbamide)

This is a summary of the risk management plan (RMP) for Xromi 100 mg/mL oral solution. The RMP details important risks of Xromi 100 mg/mL oral solution, how these risks can be minimised and how more information will be obtained about Xromi 100 mg/mL oral solution's risks and uncertainties (missing information).

Xromi 100 mg/mL oral solution's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Xromi 100 mg/mL oral solution should be used.

This summary of the RMP for Xromi 100 mg/mL oral solution should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Xromi 100 mg/mL oral solution's RMP.

I. The medicine and what it is used for

Xromi 100 mg/mL oral solution is authorised for the prevention of vaso-occlusive complications of sickle cell disease (SCD) in patients over 2 years of age.

It contains hydroxycarbamide as the active substance and it is given orally (by mouth) at a dose of 15 to 35 mg/kg/day.

Further information about the evaluation of Xromi 100 mg/mL oral solution's benefits can be found in Xromi 100 mg/mL oral solution's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/Xromi.

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

Important risks of Xromi 100 mg/mL oral solution, together with measures to minimise such risks and the proposed studies for learning more about Xromi 100 mg/mL oral solution'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 package leaflet and SmPC addressed to patients and healthcare professionals;

• Important advice on 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 (only with prescription) can help to minimise its risks.

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

In the case of Xromi 100 mg/ml oral solution, these measures are supplemented with ***additional risk minimisation measures*** mentioned under relevant important risks, below.

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

If important information that may affect the safe use of Xromi 100 mg/mL oral solution is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Xromi 100 mg/mL oral solution are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered/taken.

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 Xromi 100 mg/mL oral solution. 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);

A list of important identified/potential risks/missing information is provided in Table 1.

Table 1 List of Important Identified/Potential Risks/Missing Information

List of important risks and missing Information	
Important identified risks	1. Effects on male fertility- low sperm count (oligospermia) and absence of sperms (azoospermia) with normal shape and reduced semen volume
Important potential risks	1. Causing genetic mutation (mutagenicity) and cancer (carcinogenicity) – secondary cancers (e.g., leukaemias) 2. Off-label use in the cancer (oncology) indications not approved for this formulation (with the tablet/capsule formulation) 3. Off-label use for chronic severe anaemia (low healthy red blood cell count or low haemoglobin) – Thalassemia (a condition where the body makes an abnormal form of haemoglobin)/polycythaemia (a condition where the body makes too many red blood cells) 4. Potential medication errors – Transfer of patients from capsule and tablet to liquid formulation and two dosing syringes 5. Skin ulceration and vasculitis 6. Off-label use in children <2 years old 7. The effect on embryogenesis, teratogenic potential, breastfeeding and post-natal development 8. Safety of hydroxycarbamide in patients with underlying hepatic or renal impairment 9. Lupus erythematosus 10. Interstitial lung disease in SCD population 11. Hyperkalaemia in SCD population 12. Hyponatremia in SCD population
Missing information	1. Concurrent use of hydroxycarbamide with nucleoside analogue reverse transcriptase inhibitors and other myelosuppressive medicinal products or radiation therapy 2. Interaction with live bacterial or virus vaccines

II.B Summary of important risks

A summary of important identified/potential risks/missing information is provided in Table 2.

Table 2 **Summary of Important identified/ potential risks/ Missing information**

Important identified risk: Effects on male fertility – oligospermia and azoospermia with normal shape and reduced semen volume	
Evidence for linking the risk to the medicine	Evidence for this risk comes from published literature.
Risk factors and risk groups	Males with long-term use of Xromi 100 mg/mL oral solution in childhood or adolescence.
Risk minimisation measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures (e.g. labelling). Additional risk minimisation measures: Additional risk minimization will be undertaken by communicating this risk to physicians/healthcare providers and patients, using educational materials.
Important potential risk: Mutagenicity and Carcinogenicity – secondary cancers (e.g., leukaemias)	
Evidence for linking the risk to the medicine	Evidence for this risk comes from published literature.
Risk factors and risk groups	Children and adolescents with long-term use in SCD or long-term use of hydroxycarbamide in myeloproliferative disorders.
Risk minimisation measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures (e.g. labelling). Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Mutagenicity: None Carcinogenicity –secondary cancers (e.g. leukaemias): The open label observational, PK study will collect data if applicable
Important potential risk: Off-label use in other approved indications (oncology/cancer indications)	
Evidence for linking the risk to the medicine	Not applicable
Risk factors and risk groups	Children and adolescents with cancers or patients with difficulty swallowing.
Risk minimisation measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures (e.g. labelling). Additional risk minimisation measures: None
Important potential risk: Off-label use in chronic severe anaemia/polycythaemia/thalassemia	
Evidence for linking the risk to the medicine	Evidence for this risk comes from published literature.

Risk factors and risk groups	Children with chronic severe anaemia/polycythaemia/thalassemia.
Risk minimisation measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures (e.g. labelling). Additional risk minimisation measures: None
Important potential risk: Potential medication errors – Transfer of patients from capsule and tablet to liquid formulation and two dosing syringes	
Evidence for linking the risk to the medicine	Evidence for this risk comes from published literature and results from the bioequivalence study performed by Nova Laboratories Ltd.
Risk factors and risk groups	Use in patients to whom a capsule or tablet formulation is prescribed.
Risk minimisation measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures (e.g. labelling). Additional risk minimisation measures: Additional risk minimization will be undertaken by communicating this risk to physicians/healthcare providers and patients, using educational materials.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The open label observational, PK study will collect data if applicable

Important potential risk: Skin ulceration and vasculitis	
Evidence for linking the risk to the medicine	Evidence for this risk comes from published literature.
Risk factors and risk groups	Vascular risk factors, history of leg ulcers, diabetes.
Risk minimisation measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures (e.g. labelling). Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The Phase I/II open label observational, PK study will collect safety data on leg ulceration/infections. Final report is expected 2022.
Important potential risk: Off-label use in children <2 years old	
Evidence for linking the risk to the medicine	Not applicable.
Risk factors and risk groups	Children aged <2 years.
Risk minimisation measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures (e.g. labelling). Additional risk minimisation measures: None.
Important potential risk: The effect on embryogenesis, teratogenic potential, breastfeeding and post-natal development	
Evidence for linking the risk to the medicine	Evidence for this risk comes from published literature.
Risk factors and risk groups	Pregnant and/or breastfeeding females, female of reproductive age group and foetus or children exposed to Xromi during pre-natal period.
Risk minimisation measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures (e.g. labelling). Additional risk minimisation measures: Additional risk minimization will be undertaken by communicating this risk to physicians/healthcare providers and patients, using educational materials.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The open label observational, PK study will collect data relevant to pregnancy, if applicable
Important potential risk: Safety of hydroxycarbamide in patients with underlying hepatic or renal impairment	
Evidence for linking the risk to the medicine	Evidence for this risk comes from published literature.
Risk factors and risk groups	Patients with underlying renal impairment and hepatic impairment. Concomitant use of drugs inducing renal and hepatic impairment i.e. other chemotherapeutic agents.

Risk minimisation measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures (e.g. labelling). Additional risk minimisation measures: None.
Important potential risk: Lupus erythematosus	
Evidence for linking the risk to the medicine	Evidence for this risk comes from published literature.
Risk factors and risk groups	Patient's with abnormal immunology, long term use of hydroxycarbamide on average 5 years and above.
Risk minimisation measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures (e.g. labelling). Additional risk minimisation measures: Not applicable.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The open label observational, PK study will collect safety data on Lupus erythematosus, if applicable.
Important potential risk: Interstitial lung disease in SCD population	
Evidence for linking the risk to the medicine	Several cases of hydroxycarbamide-induced early-presenting acute pneumonitis (alveolitis and / or interstitial lung disease) late-onset lung disease (mostly fibrosis) are reported in the medical and scientific literature in patients with various myeloproliferative disorders, although none in sickle cell patients. The adverse effect is listed in the monographs of other hydroxycarbamide-containing products, e.g., Hydrea® which is indicated for myeloproliferative disorders.
Risk factors and risk groups	Not determined.
Risk minimisation measures	Not applicable.
Important potential risk: Hyperkalaemia in SCD population	
Evidence for linking the risk to the medicine	A few cases reported in patients with myeloproliferative disorder in EMA pharmacovigilance database, although none in sickle-cell patients; risk included in monographs of other hydroxycarbamide-containing products
Risk factors and risk groups	Not determined.
Risk minimisation measures	Not applicable.
Important potential risk: Hyponatremia in SCD population	

Evidence for linking the risk to the medicine	A few cases reported in patients with myeloproliferative disorders, glioma, rheumatoid arthritis or unknown indication, although none in sickle-cell patients.
Risk factors and risk groups	Not determined.
Risk minimisation measures	Not applicable.
Missing information: Concurrent use of hydroxycarbamide with nucleoside analogue reverse transcriptase inhibitors and other myelosuppressive medicinal products or radiation therapy	
Risk minimisation measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures (e.g. labelling). Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The open label observational, PK study will collect data if applicable.
Missing information: Interaction with live bacterial or virus vaccines	
Risk minimisation measures	Routine risk minimisation measures: Risks will be managed through routine pharmacovigilance practices and routine risk minimisation measures (e.g. labelling). Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The open label observational, PK study will collect data if applicable.

Abbreviations: RMP = Risk Management Plan; PASS = post authorisation safety study; PK = pharmacokinetic; SmPC = Summary of Product Characteristics, SCD = Sickle Cell Disease.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions for the approval of the marketing authorisation.

II.C.2 Other Studies in Post-Authorisation Development Plan

Nova Laboratories Ltd. plans to perform a post-authorisation study in children aged 6 months up to 18 years. This study will investigate the pharmacokinetics of the oral hydroxycarbamide solution, which will help determine the correct dosing schedule of the product in infants less than 2 years of age. The study will also check to see if the medicine is acceptable and palatable.