Summary of the Risk Management Plan

Summary of Risk Management Plan for Xromi 100 mg/mL Oral Solution (Hydroxycarbamide)

This is a summary of the risk management plan (RMP) for hydroxycarbamide. This RMP details the important risks of effects on male fertility (low sperm count and absence of sperms), secondary cancers (e.g. blood cancers such as leukaemias), off-label use (using the medicine for non-approved indication/disease) and the potential for medication errors (when changing from patients receiving tablets to receiving liquid formulation). The RMP details how these risks can be minimised and how more information will be obtained about the risks and uncertainties (missing information).

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

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 seeking authorisation to prevent complications of sickle cell disease (SCD), in adults, adolescents and children 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's benefits can be found in Xromi's EPAR, including in its plain-language summary, available on the EMA website: 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 planned study 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, is in the package leaflet and SmPC addressed to patients and healthcare professionals;
- The authorised pack size — the amount of medicine in a pack has been chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the medicine is supplied to the patient (only with prescription) to help to minimise its risks.

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 will be collected continuously and regularly analysed, reported and included in periodic safety update reports (PSURs) 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 is not yet available, it is listed under 'missing information' below.

IIA 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 2. Myelosuppression
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. Concurrent use of hydroxycarbamide with nucleoside analogue reverse transcriptase inhibitors and other myelosuppressive medicinal products or radiation therapy 8. Interaction with live bacterial or virus vaccines 9. The effect on embryogenesis, teratogenic potential, breastfeeding and post-natal development 10. Safety of hydroxycarbamide in patients with underlying hepatic or renal impairment 11. Lupus erythematosus
Missing Information	1. Influence of hydroxycarbamide in child and adolescent growth (end of puberty)

IIB 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.
Additional Pharmacovigilance Activities	Additional pharmacovigilance activities: None
Important identified risk: Myelosuppression	
Evidence for Linking the Risk to the Medicine	Evidence for this risk comes from published literature
Risk Factors and Risk Groups	Concomitant use of hydroxycarbamide and other myelosupressive medicinal products or radiation in any age group 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: 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 Phase I/II open label observational, PK study will collect haematological parameters. Final report is expected 2022.

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: 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: 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: 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: 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: 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: 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: 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 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: 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: None.

Important potential risk: Concurrent use of hydroxycarbamide with nucleoside analogue reverse transcriptase inhibitors and other myelosuppressive medicinal products or radiation therapy	
Evidence for Linking the Risk to the Medicine	Evidence for this risk comes from published literature.
Risk Factors and Risk Groups	HIV patients on retro-viral medicines, Oncology or autoimmune disorder patients on other myelosuppressive medicines.
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: Interaction with live bacterial or virus vaccines	
Evidence for Linking the Risk to the Medicine	Not applicable.
Risk Factors and Risk Groups	Concomitant use of Xromi and live virus vaccine. Concomitant use of Xromi along with other immunosuppressive drugs with live virus vaccine. Also concomitant use of Xromi and live virus vaccines in already immunocompromised patients.
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: 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: 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: 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.
Missing information: Influence of hydroxycarbamide in child and adolescent growth (end of puberty)	
Evidence for Linking the Risk to the Medicine	Results (interim) from the (non-Nova) HUSOFT extension study have shown that growth and sexual development appear to be normal and comparable to the general child population. Long-term follow-up of safety from BABY HUG (NCT00890396) and ESCORT-HU (NCT02516579) studies should be available in the literature during 2019.
Risk Factors and Risk Groups	Population 2 years and above to adolescents
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 as per protocol.

Abbreviations: BABY HUG = Long-Term Effects of Hydroxyurea in Children With Sickle Cell Anemia; ESCORT-HU = European Sickle Cell Disease Cohort – Hydroxyurea; HUSOFT = Hydroxyurea Safety and Organ Toxicity Clinical trial; RMP = Risk Management Plan; PASS = post authorisation safety study; PK = pharmacokinetic; PSUR = Periodic safety update report; SmPC = Summary of Product Characteristics.

IIC Post-Authorisation Development Plan

IIC.1 Studies Which are Conditions of the Marketing Authorisation

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

IIC.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 evaluate the efficacy/ safety of if the medicine and if it is acceptable and palatable.

Nova Laboratories Ltd. plans to perform a Health care professional Survey (questionnaire on additional risk minimisation measures) to assess the Healthcare Professionals understanding of the content of the educational materials distributed as an additional risk minimization measure.