# RISK MANAGEMENT PLAN FOR XROMI 100 MG/ML ORAL SOLUTION

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**Date for EU-RMP: 03-Sep-2025 Version 7.0**

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| α- | alpha-globin |
| ADR | adverse drug reaction |
| AE | Adverse event |
| AESIs | Adverse events of special interest |
| ATC | Anatomical Therapeutic Chemical (Classification) |
| β- | beta-globin |
| b.w. | by weight |
| CSSCD | Cooperative Study of Sickle Cell Disease |
| DNA | Deoxyribonucleic acid |
| EEA | European Economic Area |
| ESCORT-HU | European Sickle Cell Disease Cohort-Hydroxyurea |
| EU | European Union |
| FSCDR | Foundation For Sickle Cell Disease Research |
| Hb | Haemoglobin |
| HbF | Foetal haemoglobin |
| HbS | Sickle Haemoglobin |
| HbSC | Heterozygous haemoglobin SC |
| HbSS | Homozygous haemoglobin SS |
| HbSβ | Heterozygous haemoglobin with β ($\beta^0$ or $\beta^+$) thalassemia |
| HbS$\beta^0$ | Heterozygous haemoglobin with $\beta^0$ thalassemia |
| HbS$\beta^+$ | Heterozygous haemoglobin with $\beta^+$ thalassemia |
| HIV | human immunodeficiency virus |
| HU | Hydroxyurea |
| IMP | investigational medicinal product |
| INN | International Nonproprietary Name |
| LDH | Lactate Dehydrogenase |
| MA | Market authorisation |
| MAA | Marketing Authorisation Applicant |
| MAH | Marketing Authorisation Holder |
| MCV | Mean cell volume |
| MTD | Maximum tolerated dose |
| NA | Not applicable |
| NTP | National Toxicology Program |
| PL | Package Leaflet |
| PK | Pharmacokinetics |
| PASS | Post Authorisation Safety Study |
| PRAC | Pharmacovigilance Risk Assessment Committee |

| | |
|---|---|
| PSUR | Periodic safety update report |
| Q | Quarter |
| RMP | Risk management plan |
| RR | Ribonucleotide reductase |
| SCA | Sickle cell anaemia |
| SCD | Sickle cell disease |
| SmPC | Summary of Product Characteristics |
| TEAE | Treatment Emergent Adverse Event |
| QPPV | Qualified Person for Pharmacovigilance |
| UK | United Kingdom |
| US | United States |
| VOC | Vaso-occlusive crisis |

Note: The terms ‘trial’ and ‘study’ may be used interchangeably throughout.

**EU Risk Management Plan for Xromi 100 mg/ml oral solution RMP version to be assessed as part of this application:**

RMP version number:7.0

Data lock point for this RMP: 03-September-2025

Date of final sign-off: 03-September-2025

Rationale for submitting an updated RMP:

- Parts III.2 and III.3 of the RMP are updated in accordance with the *Guidance on the format of the RMP in the EU (EMA/164014/2018 Rev.2.0.1* accompanying GVP Module V Rev.2) in line with the study protocol NOVDD-001 v2.0, as submitted and approved by the EMA via EMEA/H/C/004837/II/0019. In addition to this, the updated milestones of the submitted study protocol NOVDD-001 v3.0 are also reflected in the updated RMP.

Summary of significant changes in this RMP:

- Parts III.2 and III.3 including *Table 9: Ongoing and Planned Additional Pharmacovigilance Studies* are updated in accordance with the Guidance on the format of the RMP in the EU (*EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2*) in line with the approved study protocol NOVDD-001, v2.0, and the submitted study protocol NOVDD-001, v3.0.

**Details of the currently approved RMP:**

Version number: **6.1**

Approved with procedure: **EMEA/H/C/004837/IB/0024**

Date of approval (opinion date): **16-Sep-2024**

**Name of EU Qualified Person for Pharmacovigilance (QPPV):**

QPPV Name: Dr. Michael Bernstein

QPPV Signature:

# PART I PRODUCT OVERVIEW

## Table 1 Product Overview

| | |
|---|---|
| **Active Substance(s) (INN) or common name:** | Hydroxycarbamide |
| **Pharmacotherapeutic group(s) (ATC code(s)):** | L01XX05 |
| **Marketing Authorisation Holder or Applicant:** | Lipomed GmbH |
| **Medicinal products to which this RMP refers:** | Xromi 100 mg/mL oral solution |
| **Invented name(s) in the European Economic Area (EEA):** | Xromi 100 mg/mL oral solution |
| **Marketing authorisation procedure:** | Centralised |
| **Brief description of product including:** | |
| **Chemical class:** | Hydroxycarbamide, a ribonucleotide reductase inhibitor, is a cytotoxic, antimetabolite, antineoplastic agent. |
| **Summary of mode of action** | The specific mechanism of action of hydroxycarbamide is not fully understood. Hydroxycarbamide's mode of action is complex and can be generally categorised into two overlapping pathways: effects on foetal haemoglobin (HbF) production and improved blood flow through reduced intercellular adhesion. The primary effect of hydroxycarbamide is to increase HbF levels. HbF inhibits intracellular sickle haemoglobin polymerisation and prevents the sickling process within erythrocytes. The principle and most well understood mechanism of action of hydroxycarbamide *in vivo* is the reversible inhibition of ribonucleotide reductase (RR), a critical enzyme that converts ribonucleosides into deoxyribonucleosides, which are required for the synthesis and repair of deoxyribonucleic acid. Potent inhibition of RR leads to decreased intracellular pools of deoxyribonucleotide triphosphates and impedes progression of cellular division through S phase. Temporary arrest of haematopoiesis through once-daily hydroxycarbamide results in altered erythroid kinetics; upon recovery such 'stress erythropoiesis' features higher HbF through recruitment of early erythroid |

| | |
|---|---|
| | progenitors that maintain their HbF-producing capacity. Erythrocytes with more HbF are larger (higher mean corpuscular volume) and more deformable (better rheology).<br>Recently, hydroxycarbamide has shown to be associated with the generation of nitric oxide suggesting that nitric oxide stimulates cyclic guanosine monophosphatase production, which then activates a protein kinase and increases the production of HbF. Other known pharmacological effects of hydroxycarbamide which may contribute to its beneficial effects in sickle cell disease include decrease of neutrophils, increase of the water content of erythrocytes, increase of the deformability of sickled cells, and altered adhesion of red blood cells to the endothelium. |
| **Important information about its composition** | Hydroxycarbamide is an odourless or almost odourless, tasteless white to off-white crystalline solid. Chemical formula of hydroxycarbamide: $CH_4N_2O_2$, molecular weight: 76.05.<br>The proposed oral formulation contains excipients which are commonly used in pharmaceutical formulations namely methyl hydroxybenzoate, sucralose, strawberry flavour, sodium hydroxide, xanthan gum (Xantural® 75), and water for irrigation. |
| **Hyperlink to the Product Information** | Module 1.3.1 |
| **Indication(s) in the EEA:** | |
| **Current:** | Xromi is indicated for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 9 months of age. |
| **Proposed:** | Not applicable |
| **Dosage in the EEA:** | |
| **Current:** | The posology should be based on the patient's body weight (kg).<br>The usual starting dose of hydroxycarbamide is 15 mg/kg/day and usual maintenance dose is between 20-25 mg/kg/day. The maximum dose is 35 mg/kg/day. Full blood cell count with white cell differential and reticulocyte count |

| | |
|---|---|
| | should be monitored once a month for the first 2 months following treatment initiation. |
| **Proposed:** | Not applicable |
| **Pharmaceutical form(s) and strength(s):** | |
| **Current:** | Oral solution 100 mg/mL |
| **Proposed:** | Not applicable |
| **Is/will the product be subject to additional monitoring in the EU?** | No |

Abbreviations: ATC = Anatomical Therapeutic Chemical; EEA =European Economic Area; EU = European Union; INN = International Nonproprietary Name; HbF = Haemoglobin (Foetal); RMP = Risk management plan; RR = Ribonucleotide reductase.

# PART II SAFETY SPECIFICATION

## MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATIONS

Active substance(s): Hydroxycarbamide

Product(s) concerned: Xromi 100 mg/mL oral solution

MAH name: Lipomed GmbH.

Data lock point for this module: 28-Jun-2023

RMP version number when this module was last updated: 4.3

**Indication:** The previous MAH, Nova Laboratories Ltd. has developed a novel oral solution formulation of hydroxycarbamide (hydroxyurea), which overcomes the serious limitations with the currently available oral dosage forms and satisfies an unmet clinical need for patients. Xromi 100 mg/mL oral solution is indicated, for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 9 months of age.

**Incidence:** New-born estimates consistently suggest that approximately 300,000 babies per year are born with sickle cell anaemia (SCA), with the majority in Nigeria, the Democratic Republic of the Congo and India (Piel et al., 2013). In the European Union (EU), based on registers, publications, extrapolation from SCD birth rates and the Orphanet Database, it is estimated that SCD is likely to affect up to 1.5 in 10,000 people. Population estimates in the United States (US) suggest that a total of approximately 100,000 persons have the disease (Hassell 2010). For any other country, neither a reliable, all-age for country-specific estimate nor a global estimate exists (Piel et al., 2017) for SCD. SCD is estimated to occur in one out of every 365 Black or African-American births and one out of every 16,300 Hispanic-American births; one in every 13 Black or African-American babies is born with sickle cell trait (Centers for Disease Control 2016).

**Prevalence:** SCD is a multisystem disease, associated with episodes of acute illness and progressive organ damage and is one of the most common severe monogenic disorders worldwide.

SCD is used to refer to all the different genotypes that cause the characteristic clinical syndrome. SCD and thalassemia are genetic disorders caused by the abnormal gene inheritance for haemoglobin. Inheritance can be a single gene from each parent leading to homozygous sickle cell (HbSS type), inheritance of the S gene (HbS) from one parent and the C gene from another parent (leading to HbSC type) or inheritance of only the S gene from one of the parent and a normal haemoglobin gene from another parent (leading to sickle cell trait). Thalassemia is the inheritance of a disorder leading to a defect in the alpha- (α-) or beta- (β-) globin chains of haemoglobin leading to α- or β-thalassemia. The combination of the sickle cell mutation and beta-thalassemia mutation gives rise to a compound heterozygous condition known as HbSβ-thalassemia.

The most prevalent genotypes of abnormal haemoglobin include HbSS and the compound heterozygous conditions haemoglobin $S\beta^0$-thalassemia (Hb-$S\beta^0$-thalassemia), haemoglobin $S\beta^+$-thalassemia (Hb$S\beta^+$-thalassemia) and HbSC. HbSS and Hb $S\beta^0$ thalassemia genotypes are associated with the most severe clinical manifestations and are commonly referred to as SCA.

In 2010 there were approximately 300,000 new-borns born worldwide with HbSS with over half of these born in Nigeria, Democratic Republic of Congo and India (Piel et al., 2013). The prevalence of SCD is highest in Sub-Saharan Africa. Lack of diagnostic facilities means that precise data are not available; however, it is estimated that more than 230,000 affected children are born in this region every year (0.74% of the births in Sub-Saharan Africa), which is about 80% of the global total. By comparison, the yearly estimate of affected births in Europe is 1300 and in North America is 2600 (Modell and Darlison 2008). In populations of African ethnic origin, SCA typically accounts for 70% of cases of SCD, with most of the remainder having HbSC disease (Nagel et al., 2003).

Driven by the selective advantage of heterozygous individuals against *Plasmodium falciparum* infection, HbS was historically only found in Sub-Saharan Africa, the Mediterranean area, the Middle East and India. In contrast, these genetic traits are quite rare in the western, central and northern countries of the European continent and in Europe. It was endemic only in Greece and southern Italy (Roberts and De Montalembert, 2007). Because they are endemic or have expanded following migration flows to and within the EU, SCD are present in all European countries creating an important impact on health services. However, there are still poor data on the precise prevalence, overall burden and trends of the diseases, due to a lack of comprehensive data collection and analysis systems in the different European countries (Martinez et al., 2014).

Data on the prevalence of SCD within individual EU countries have come from a variety of sources: national registries, direct communication with named contacts through the Orphanet website, journal publications, national reports and extrapolations based on estimated annual number of SCD births in the member states.

There have been many national and local initiatives in European countries to obtain accurate, up-to-date measures of the changing prevalence of SCD, although attempts to establish comprehensive national registries have so far largely failed, despite individual efforts, because of insufficient funding. Presently, national SCD registries are only available for Belgium, Greece and the United Kingdom (UK). Local or regional registries exist in France, Italy and the Netherlands (Roberts and De Montalembert 2007).

Modell et al. (2007) calculated the estimated proportions of residents and births in non-indigenous populations at risk of haemoglobin disorders (SCD and thalassemias) in Western, Northern and Southern Europe together with Turkey. These estimates showed that the highest proportions of the population carrying HbS were seen in Albania (3.0%), France (0.6%), Portugal (0.57%), Greece (0.53%), the Netherlands (0.47%), England and Wales (0.47%) and Turkey (0.44%). This compares with only 0.01% in Scotland, 0.02% in Finland and 0.08% in Ireland. The highest numbers of carriers were seen in France, England/Wales

and Turkey which were all estimated to have >200,000 HbS carriers; the total number of carriers in Europe was almost 1.5 million (Roberts and de Montalembert. 2007).

Estimating the prevalence of SCD is fraught with incomplete and inconsistent data and reporting. In the EU, based on prevalence from a number of perspectives (registers, publications, extrapolation from SCD birth rates and the report on the Orphanet Database) SCD prevalence rate in the EU is likely to be up to 1.5 in 10,000. Population estimates in the US suggest that a total of approximately 100,000 persons have the disease (Hassell 2010).

**Demographics of the Population in the Authorised/Proposed Indication:** The approved indication for Xromi 100 mg/mL oral solution is in adults as well as adolescents and children from the age of 2 years in the EU and this indication has been extended to patients> 9 months of age. Although certainly a rare disease because of its lower frequency in the 28 countries of the EU, SCD is the most prevalent genetic disease in France and the UK and its frequency is steadily rising in many other countries in Northern, Central and Southern Europe (Colombatti and Sainati, 2016). Regional variation in the frequency of HbS within the endemic countries of origin leads in turn, through the settling of immigrant populations in localised groups, to foci of high prevalence in their adopted countries (e.g. London, Birmingham, Paris, Brussels, Madrid and Copenhagen) with consequent implications for screening and service provision (Roberts and de Montalembert 2007).

Population estimates in the US suggest that a total of approximately 100,000 persons have the disease (Hassell 2010). SCD occurs among about one out of every 365 Black or African-American births and one out of every 16,300 Hispanic-American births; and one in every 13 Black or African-American babies is born with sickle cell trait.

**Risk Factors:** SCD is an inherited monogenic recessive disorder, caused by a mutation in a blood protein called haemoglobin. It is inheritance of an abnormal gene from either or both of the parents. Absence of SCD awareness and pre-marriage genetic counselling in the geographical area where SCD is more prevalent will have more risk for the inheritance of SCD or the severe form of SCD (Modell et al., 2007; Modell and Darlison 2008). Risk factors for relating to important co-morbidities are discussed below.

**Main Existing Treatment Options:** Currently available treatments include transfusions and hydroxycarbamide, although stem cell transplantation might be a potentially curative therapy (Ware et al., 2017). Penicillin prophylaxis and anti-pneumococcal vaccination have also significantly decreased the incidence of life-threatening infections in children with SCD in regions in which these treatments are utilised. In many European countries and the US, diagnosis is now made at birth with new-born bloodspot screening (Telfer et al., 2015). New-born screening programs are slowly being initiated in parts of Africa, including Ghana, but many affected individuals are still without access to these necessary prevention measures (Kanter and Kruse 2013). A summary of available treatments are presented below:

***Hydroxycarbamide (also known as Hydroxyurea [US Adopted Name]):*** Hydroxycarbamide is a cytotoxic, antimetabolite and antineoplastic agent used for several decades to treat a variety of medical disorders, most notably myeloproliferative neoplasms, chronic myelogenous leukaemia and human immunodeficiency virus (HIV). The first clinical application of

hydroxycarbamide for patients with SCA was reported by Platt et al. (1984), who demonstrated a rapid and dramatic increase in foetal haemoglobin (HbF)-containing reticulocytes without significant bone marrow toxicity.

Over the last 30 years hydroxycarbamide has become established as a disease modifying therapy following a series of 'proof of principle' experiments, Phase I to III studies in adults and children with SCA treated with hydroxycarbamide (McGann and Ware, 2011). Through these studies, hydroxycarbamide has demonstrated significant dose-dependent increases in haemoglobin and HbF along with concurrent reduction in total white blood cells, neutrophils, reticulocytes and reduction in haemolysis.

Hydroxycarbamide was approved for the treatment of adults with SCD by the Food and Drug Administration in 1997 and for both children and adults by the European Medicines Agency in 2006.

Hydroxycarbamide has been shown to reduce or prevent several SCD complications and is presently the only approved, disease modifying agent available in the EU.

In the EU, Siklos® (hydroxycarbamide) tablets (100 and 1,000 mg) are indicated for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in adults, adolescents and children older than 2 years suffering from symptomatic SCD. Due to the low number of patients with SCD, the disease is considered 'rare' and Siklos® was designated an 'orphan medicine' (a medicine used in rare diseases) on 09 Jul 2003. The starting dose is usually 15 mg/kg, using the most appropriate tablet strengths (100 or 1,000 mg) to make up the dose, breaking up the 1,000 mg tablet in quarters (250 mg) if needed. The dose is adjusted according to the response to treatment, with the usual dose being between 15 and 30 mg/kg/day. Doses of up to 35 mg/kg/day can be used in exceptional cases. The most common side effect with Siklos® (>1/10 patients) is bone marrow suppression, causing neutropenia, reticulocytopenia and macrocytosis. In men, reversible oligospermia or azoospermia is also very commonly seen.

There are currently no approved SCD modifying agents for children under the age of 2 years.

***Red Blood Cell Transfusions:*** An estimated 90% of adults with SCD receive at least one transfusion in their lifetimes (Chou, 2013). Physicians may use acute transfusions for immediate benefits, such as increased oxygen-carrying capacity and improved blood flow or chronic transfusions to help prevent long-term complications (Ware et al., 2017). A transfusion helps to raise the number of red blood cells and provides normal red blood cells that are more flexible than red blood cells with sickle haemoglobin. These cells live longer in the circulation. Red blood cell transfusions decrease vaso-occlusion and improve oxygen delivery to the tissues and organs.

Blood transfusions are helpful in SCD and can be life-saving in certain acute settings, but have many short- and long-term complications, including acute transfusion reactions, transmission of infection, the development of allo- and auto-antibodies to erythrocyte antigens and severe transfusion-acquired iron overload leading to further damage to organs such as the heart, pancreas and liver.

***Haematopoietic Stem Cell Transplantation:*** Currently most SCD transplants are performed in children who have had complications such as strokes, acute chest crises and recurring pain crises. These transplants usually use a matched donor. Because only about 1 in 10 children with SCD has a matched donor without SCD in their families, the number of people with SCD who receive transplants is low. Haematopoietic stem cell transplantation is successful in about 85% of children when the donor is related and human leukocyte antigen matched.

Haematopoietic stem cell transplantation is more risky in adults, hence why most transplants are done in children. Complications can include severe infections, seizures and other clinical problems. About 5% of people have died.

Stem cell transplantation can be curative for SCA but is extremely limited as a practical therapy even in high resource settings due to lack of matched donors, high cost and concern about long-term effects including death and sterility (McGann and Ware 2015).

**Natural History of the Indicated Condition in the Untreated Population, including Mortality and Morbidity:**

SCD is an inherited monogenic recessive disorder, caused by a mutation in haemoglobin. Historically SCD was only found in Sub-Saharan Africa, the Mediterranean area, the Middle East and India, but has spread globally, in part, due to migration. In many European countries and the US, diagnosis is now made at birth with new-born bloodspot screening. Identifying SCD infants early by neonatal screening reduces morbidity and mortality. However, some older children are still diagnosed after presenting with crisis, or diagnosed as an incidental finding from family studies or pre-operative testing. These are generally very mildly affected children who have moved to the country from Africa or elsewhere during childhood. A neonate with HbSS will have about 90% HbF, 10% HbS and no detectable adult haemoglobin (Telfer et al., 2015).

Similarities/ differences in children and adults

SCD is the quintessential multi-organ disease in which patients experience a range of symptoms and complications, which begin in infancy and progressively worsen with age. Hence children and adults experience many of the same symptoms, but with disease progression with age, adults will develop additional disease manifestations such as leg ulcers, chronic renal failure, heart failure and pulmonary hypertension.

Some of the common chronic problems in children often highlighted during out-patient visits include fatigue, headaches and nocturnal enuresis. Their aetiology is related to the pathological effects of SCD. Management of these problems is challenging and general paediatric protocols are often poorly effective (Telfer et al., 2015).

*Infants and Children*

Infants with SCD can present with symptoms beginning at 6 months of age (as foetal haemoglobin dissipates) with dactylitis (painful swelling of the hands or feet), anaemia, mild jaundice, or an enlarged spleen (Table 2). The most frequent problems seen in paediatric SCD

are pain, infection, acute splenic sequestration, ACS, and stroke. Poor splenic function results in a compromised immune system and increased susceptibility to infection (including sepsis), which is the primary cause of mortality in paediatric patients. Penicillin prophylaxis and anti-pneumococcal vaccination have significantly decreased the incidence of life-threatening infections in children with SCD in regions in which these treatments are utilized (Kanter et al, 2013).

*Adults*

Adults with SCD experience many of the same symptoms as children. However, additional disease manifestations may present or worsen as patients age, including leg ulcers, sickle retinopathy, nephropathy, decreased bone density, thromboembolic complications, pulmonary hypertension, cardiac failure, transfusional iron overload, and avascular necrosis (Table 2). Causes of death in adults with SCD are more variable than in children and include infection, ACS, pulmonary emboli, liver failure (due to iron overload), stroke, and heart failure. For adults with SCD, vaso-occlusive crisis (VOC) is the leading admission diagnosis and the main reason for emergency department visits. Currently, in the UK, people with SCD typically live until 40-60 years of age, although milder types of sickle cell disease may have no impact on life expectancy (NHS UK website).

The Clinical manifestations of paediatric and adult SCD are summarised in Table 2.

**Table 2: Clinical Manifestations of Paediatric and Adult Sickle Cell Disease (Kanter et al, 2013)**

| | **Paediatric SCD** | | **Adult SCD (additional signs and complications to those seen in children)** |
|---|---|---|---|
| Signs and Symptoms | | | |
| | Infants | Children | |
| | Pain in chest, abdomen and limbs/joints<br>Dactylitis<br>Anaemia<br>Mild Jaundice<br>Enlarged spleen<br>Fever<br>Frequent upper respiratory tract infections | Pain (acute or chronic)<br>Acute anaemia<br>Infections<br>Jaundice<br>Poor nutritional status and growth<br>Academic failure<br>Delayed puberty | Severe joint pain<br>Chronic leg ulcers<br>Retinopathy<br>Thromboembolic complications<br>Neurocognitive impairments<br>Opioid dependence/tolerance |
| Complications | | | |
| Central Nervous System | Stroke | | Recurrent ischemic stroke, haemorrhagic stroke |
| Eye | Retinal artery occlusion/retinopathy | | Progressive retinopathy |
| Lung | Acute Chest Syndrome (ACS)<br>Asthma | | Recurrent ACS<br>Pulmonary hypertension<br>Chronic lung disease |
| Heart | Left ventricular hypertrophy<br>Cardiomyopathy | | Premature coronary artery disease<br>Heart Failure |
| Spleen | Acute splenic sequestration<br>Auto-infarction<br>Impaired immunity (e.g. Bacterial infections, sepsis) | | Functional asplenia |
| Liver | | | Hepatic sequestration<br>Liver failure due to transfusional iron overload |
| Kidney | Hyposthenuria<br>Proteinuria<br>Renal impairment/failure | | Frequent urinary tract infections |
| Gall Bladder | Cholelithiasis | | Cholelithiasis |
| Genitals | Priapism | | Priapism |
| Bones/joints | Avascular necrosis<br>Aplastic crisis | | Avascular necrosis<br>Aplastic crisis |
| Skin | Chronic ulcers | | Chronic ulcers |

Since SCD is a lifelong disease, the duration of the disease is replaced by life expectancy. Overall, the life expectancy for SCD tends to be much shorter than normal but this can vary

depending on the specific genotype, access to healthcare, adherence to medical interventions and strong and long-term family support. Currently, people with HbSS or HbS$\beta^0$ SCA (the most common and severe genotypes) typically have a life expectancy of 40 to 60 years of age, although milder types of SCD (e.g. HbSC) may have no impact on life expectancy (Lanzkron et al., 2013).

The life expectancy of children has improved dramatically, with current estimated survival of up to 97% at age 16 (Telfer et al., 2015). Some of the improvement in survival in SCD over the past few decades has been attributed to neonatal screening, facilitating early access to prophylaxis with penicillin, comprehensive care including disease modifying therapies (e.g. transfused blood and hydroxycarbamide) and parental education on the early detection of complications such as acute splenic sequestration (Rees et al., 2010).

Due to the limited follow-up, mortality is difficult to assess in randomised controlled trials. However, results from four prospective observational studies with large sample size (two in adults, two in children) indicate a survival advantage for patients receiving hydroxycarbamide (Lobo et al., 2013; Voskaridou et al., 2010; Steinberg et al., 2010, Lê et al., 2015).

**Important Co-morbidities:** SCD shows considerable phenotypic heterogeneity resulting from both genetic and environmental factors. It is a multi-organ disease, in which patients experience a range of symptoms and complications that worsen with age.

The most frequent problems seen in paediatric SCD are pain, infection, acute splenic sequestration, acute chest syndrome and stroke. Poor splenic function results in a compromised immune system and increased susceptibility to infection (including sepsis), which is the primary cause of mortality in paediatric patients.

Infants with SCD can present with symptoms from 6 months of age (as foetal haemoglobin dissipates) such as dactylitis, anaemia, mild jaundice, or an enlarged spleen.

Adults with SCD experience many of the same symptoms as children. However, additional disease manifestations may present or worsen as patients age, including leg ulcers, sickle retinopathy, nephropathy, decreased bone density, thromboembolic complications, pulmonary hypertension, cardiac failure, transfusional iron overload and avascular necrosis. Causes of death in adults with SCD are more variable than in children and include infection, acute chest syndrome, pulmonary emboli, liver failure (due to iron overload), stroke and heart failure. For adults with SCD, vaso-occlusion episode is the leading admission diagnosis and the main reason for emergency department visits. Acute pain episodes peak at age 20 to 29 years and, in one study, adults reported pain on more than 50% of days, with severe SCD-related pain reducing quality of life. Adult patients who report more than three pain crises per year have a predicted decreased survival. Strokes in adults with SCD tend to be severe, with ischaemic stroke (most frequent between 35 and 65 years of age) often causing physical and cognitive disability and haemorrhagic stroke (most frequent in young adults) having a high mortality rate (Kanter and Kruse 2013).Other complications include avascular necrosis of the femoral head, proliferative retinopathy, cholelithiasis, sickle hepatopathy and priapism. Some of the common

chronic problems in children often highlighted during out-patient visits include fatigue, headaches and nocturnal enuresis. Their aetiology is related to the pathological effects of SCD. Management of these problems is challenging and general paediatric protocols are often poorly effective (Telfer et al., 2015).

Summaries of the most common co-morbidities are presented below:

***Vaso-Occlusive Crisis and Acute Pain***

A vaso-occlusive crisis is a common painful complication of SCA; it is also the most common form of sickle cell crisis.

Infants with SCD may develop hand-foot syndrome, a dactylitis presenting as exquisite pain and soft tissue swelling of the dorsum of the hands and feet. The syndrome develops suddenly and lasts one to two weeks. Hand-foot syndrome occurs between 6 months and 3 years of age; it is not seen in patients older than 5 years because haematopoiesis in the small bones of the hands and feet ceases at this age (Maakaron and Besa 2015).

Vaso-occlusion may result in not only recurrent painful episodes but also a variety of serious organ system complications that can lead to lifelong disabilities and/or early death. For example, based on data from the Cooperative Study of SCD, in which the circumstances of death were examined in 209 patients who were over 20 years old at the time of death, 22% occurred during a pain episode (Farber et al., 1985).

Acute pain is the most common reason for admission to hospital for both adults and children, although it is more common in teenagers and young adults than in young children. Although acute vaso-occlusive pain is typically self-limiting and does not result in permanent organ damage, it is the most important complication from the patient's perspective and increased frequency of pain is associated with early death in patients with SCA who are older than 20 years. Frequent episodes of acute pain are associated with SCA (compared with HbSC disease), high haematocrit, low HbF concentrations, sibling history of asthma and nocturnal hypoxaemia. Opiate analgesia is the mainstay in the management of severe pain. (Rees et al., 2010).

Traditional treatments include opioids, non-steroidal anti-inflammatory drugs and hydration. Hydroxycarbamide (discussed above), although not helpful for acute relief, can decrease the number of painful episodes when taken chronically. Relaxation techniques, warmth, massage and psychological pain management (e.g. cognitive behavioural therapy) should also be considered (Kanter and Kruse 2013).

***Infections***

Bacterial infections are a major cause of morbidity and mortality in children with SCD. The increased susceptibility of affected children is likely to result from several causes, including impaired splenic function, defects in complement activation, micronutrient deficiencies and tissue ischaemia. Several organisms, including *Streptococcus pneumoniae*, *Haemophilus influenza* and non-typhi *Salmonella* species, have been identified as important causes of infection in developed countries. The introduction of penicillin prophylaxis and

immunisation with conjugate vaccines directed against *S. pneumoniae* and *H. influenza* type b have improved the prognosis (Rees et al., 2010).

***Neurological complications***

Neurological complications of SCA are one of the most common causes of stroke in children. Irregular, sporadic episodes of ischaemic brain injury are known to occur in SCA, resulting in overt stroke and silent cerebral infarction. Quinn et al. (2013) report that children with SCA experience ongoing (chronic, intermittent) cerebral ischaemia, which is sometimes reversible, far more frequently than previously recognised.

The Cooperative Study of Sickle Cell Disease (CSSCD) is the largest longitudinal study of patients with SCD, observing a cohort of more than 4,000 adults and children. The study found an overall stroke prevalence of 3.75% (Ohene-Frempong et al., 1998). Stroke incidence varies significantly between the different sickle cell genotypes, with the highest frequency in those with the homozygous HbSS genotype (Ohene-Frempong et al., 1998, Powars et al., 1978). The highest incidence of ischaemic stroke in HbSS patients was in children aged 2 to 9 years, with a second peak after the age of 30 years. In contrast, the incidence of haemorrhagic stroke peaked at ages 20 to 29 years and very rarely occurred in children or adults outside of this age range (Ohene-Frempong et al., 1998). While these early studies suggested a predisposition to stroke in early childhood, a retrospective database review of patients with SCD from California showed that the overall highest incidence of ischaemic stroke was in middle-aged adults aged 35 to 64 years and elderly adults aged 65 years and older, with stroke risk being threefold higher in middle-aged patients with SCD than in the general African-American population (Strouse et al., 2009). Importantly, the CSSCD study showed an overall 14% recurrence rate of stroke in HbSS patients with a much higher rate in those who had an initial cerebrovascular accident at <20 years of age. Patients with HbSS disease are calculated to have a 24% chance of stroke by 45 years of age (Ohene-Frempong et al. 1998).

***Splenic Sequestration Crisis***

Because of the spleen's narrow vessels and function in clearing defective red blood cells, the spleen is frequently affected in SCD. It is usually infarcted before the end of childhood in individuals suffering from SCA. Splenic sequestration crises will present as acute, painful enlargements of the spleen, caused by intrasplenic trapping of red cells. This can ultimately result in a dangerous fall in haemoglobin levels creating the potential for hypovolemic shock. Sequestration crises are considered an emergency. If untreated, patients may die within one or two hours due to circulatory failure (Rees et al., 2010).

***Acute chest syndrome***

Acute chest syndrome is the second most common complication and cause of hospital admission in patients with SCD. It is also the second most common cause of death in patients with SCD, accounting for approximately 25% of deaths. This syndrome is caused by a combination of infection, fat embolism and vaso-occlusion of the pulmonary vasculature. Fifty percent of adult patients experience pain exacerbation within two weeks prior to the acute chest syndrome (Vichinsky et al., 1997). Severity varies but 13% of patients require mechanical

ventilation and 3% die. Treatment involves broad-spectrum antibiotics, bronchodilators and oxygen. If haemoglobin concentrations decrease substantially or the patient's clinical condition deteriorates, blood transfusion is commonly given (Rees et al., 2010).

***Pulmonary hypertension***

Pulmonary hypertension is an increasingly recognised complication of SCD in teenagers and adults. Risk factors such as hypoxaemia, sleep apnoea, pulmonary thromboembolic disease, restrictive lung disease, left ventricular systolic and diastolic dysfunction, severe anaemia and iron overload need to be identified and treated (Rees et al., 2010). It has been suggested that pulmonary hypertension may be a complication of chronic haemolysis seen in SCD. Pulmonary hypertension is associated with an increased risk of death (Aliyu et al., 2008, Gladwin et al., 2004, Gladwin and Sachdev, 2012).

***Heart disease***

Left-sided heart disease occurs in about 13% of adults with SCD and is mainly caused by diastolic dysfunction; systolic dysfunction can also occur and valvular disease is present in about 2% of patients. The presence of diastolic dysfunction alone in patients with SCD is an independent risk factor for mortality. Patients with both pulmonary vascular disease and diastolic dysfunction are at a particularly high risk of death (odds ratio for death 12.0, 95% CI 3.8 to 38.1, p<0·001). Pulmonary pressures rise acutely during vaso-occlusive pain and even more during acute chest syndrome. In a study, 13% of patients manifested right heart failure with acute chest syndrome and this subgroup had the highest risk of mechanical ventilation and death (Rees et al., 2010).

A study by Nicholson et al., 2011 also indicated that coronary artery dilation is common in children with SCD. The prevalence of coronary artery ectasia in patients with SCD was 17.7%, compared with 2.3% for the general population. Furthermore, a systolic murmur is usually present, with wide radiation over the precordium (Maakaron and Besa 2015).

***Aplastic Crisis***

Aplastic crises are acute worsening of the patient's baseline anaemia, which may cause pallor, tachycardia and fatigue. This crisis is normally triggered by the human parvovirus B19, a fairly common deoxyribonucleic acid virus. A B19 infection directly affects production of red blood cells by invading the red cell precursors and multiplying in the precursor cells, ultimately destroying them. Parvovirus infection nearly completely prevents red blood cell production for 2 to 3 days. In normal individuals, this is of little consequence; however, the shortened red cell life in SCA patients results in an abrupt and potentially life-threatening situation. Reticulocyte counts drop dramatically during the crisis and the rapid turnover of red cells may lead to a drop in haemoglobin. An aplastic crisis often lasts 4 days to a week before resolving (Serjeant 2010).

***Renal complications***

Renal damage is almost inevitable in SCD. About 25% of patients with SCA have renal insufficiency (defined as a reduced creatinine clearance of < 90 mL/min) and 30% of adults develop chronic renal failure, which is a contributory factor in many deaths (Rees et al., 2010).

Approximately 15% of patients will advance to end stage renal disease by the third decade of their life (Guasch et al., 2006).

***Avascular Necrosis***

SCD is the most common cause of avascular necrosis of the hip in paediatric patients. By the age of 35 years, avascular necrosis has been reported to occur in as high as 41% of patients with SCA. Although it is primarily diagnosed with magnetic resonance imaging, some authors suggest the true prevalence is unknown. Surgical treatment with coring and osteotomy and joint replacement has been used in cases of severe disease. Unfortunately, SCD patients have had particularly poor results with hip replacement, with up to 59% failing within 6 years (Styles and Vichinsky 1996).

***Effects on Growth and Maturation***

During childhood and adolescence, SCD is associated with growth retardation, delayed sexual maturation and being underweight. Rhodes et al. (2009) demonstrated that growth delay during puberty in adolescents with SCD is independently associated with decreased haemoglobin concentration and increased total energy expenditure.

Their results showed that children with SCD progressed more slowly through puberty than healthy control children. Affected pubertal males were shorter and had significantly slower height growth than their unaffected counterparts, with a decline in height over time; however, their annual weight increases did not differ. In addition, the mean fat free mass increments in affected males and females were significantly less than those of the control children.

***Cholelithiasis***

Cholelithiasis is common in children with SCD, as chronic haemolysis with hyperbilirubinaemia is associated with the formation of bile stones. Cholelithiasis may be asymptomatic or result in acute cholecystitis, requiring surgical intervention. The liver may also become involved. Cholecystitis or common bile duct obstruction can occur (Maakaron and Besa 2015).

***Eye Involvement***

Paraorbital facial infarction may result in ptosis. Retinal vascular changes also occur. A proliferative retinitis is common in HbSC disease and may lead to loss of vision (Maakaron and Besa 2015).

***Leg Ulcers***

Leg ulcers are a chronic, painful problem. They result from minor injury to the area around the malleoli. Because of relatively poor circulation, compounded by sickling and micro-infarcts, healing is delayed and infection becomes established (Maakaron and Besa 2015).

**MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION**

Active substance(s): Hydroxycarbamide

Product(s) concerned: Xromi 100 mg/mL oral solution

MAH name: Lipomed GmbH.

Data lock point for this module: 16 Apr 2019

RMP version number when this module was last updated: 1.0

This section is not applicable.

**MODULE SIII CLINICAL TRIAL EXPOSURE**

Active substance(s): Hydroxycarbamide

Product(s) concerned: Xromi 100 mg/mL oral solution

MAH name: Lipomed GmbH.

Data lock point for this module: 11-Nov-2022

RMP version number when this module was last updated: 4.1

**Clinical Trial Exposure History**

The role of hydroxycarbamide in the treatment and disease modification of sickle cell has been established over almost 30 years through a number of randomised controlled trials and observational studies. In the United States (US), hydroxycarbamide capsules (Droxia®, Bristol-Myers Squibb) are indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in adult patients with sickle cell anaemia. Hydroxycarbamide in a capsule form (Hydrea®) has been licensed and marketed in the European Union (EU) for the treatment of neoplastic disease for many decades. In addition, hydroxycarbamide in a tablet form (Siklos®) was approved in the EU in 2007 for the prevention of symptoms associated with sickle cell disease in adults and children over the age of 2 years.

Approval of Xromi 100 mg/mL oral solution was based on a single-center, single-dose, open-label, randomised, three-period crossover trial to assess the bioequivalence of an oral hydroxycarbamide solution 500 mg/5 mL versus 2 formulations of oral hydroxycarbamide capsule 500 mg (Hydrea®) in 30 healthy adult subjects under fasting conditions. Each subject was due to receive a single-dose of each of the following investigational medicinal products (IMPs) over 3 treatment periods in accordance with the randomisation schedule (one IMP/period): Xromi oral solution (500 mg/5 mL), Hydrea® 500 mg capsule (UK) and Hydrea® 500 mg capsule (United States [US]): INV490 BE.

Post-approval, the MAH conducted a prospective open label, PK study of Xromi solution in children with sickle cell anaemia, aged from 6 months to 17.99 years (i.e. to the day before 18th birthday), with a 12- to 15-month treatment period for each participant. The study treatment duration was for 6 months at the maximum tolerated dose (MTD), which was usually reached by 6 months after initiation of treatment. For study participants in whom time to MTD was longer than 6 months or not achieved at all, the maximum duration of study treatment was 15 months. All study participants started on an oral dose of 15 mg/kg once daily. The dose was escalated by 5 mg/kg/day every 8-12 weeks until the MTD was achieved (defined as occurrence of haematological toxicity, an ANC of 1-3 ×109/L, or a maximum dose of 35 mg/kg/day). Once the MTD was established, treatment was maintained for a maximum of 12-15 months. The trial was finalised (LPLV) 29 December 2021.

The exposure for the clinical programme (all treatment arms) and exposure by age, gender and race for Xromi is provided in the tables below. In total, 63 subjects have been enrolled into clinical trials, of which 60 subjects have been exposed to Xromi.

Exposure based on age group, gender and ethnic origin are presented in Table 3, Table 4, and Table 5.

### Clinical Trial Exposure Data

**Table 3 Subject Exposure to Xromi in the Development Programme**

| Treatment | Number of Subjects |
|---|---|
| **Bioequivalence trial (RD 729/26118) (INV490 BE)[a]** | |
| Xromi Oral Solution | 28 |
| Hydrea® (UK) | 30 |
| Hydrea® (US) | 29 |
| **Paediatric trial (INV543)** | |
| Xromi Oral Solution | 32[b] |
| **Total[a]** | **60** |

Abbreviations: UK = United Kingdom; US = United States.

[a]A total of subjects were 30 subjects were enrolled into the INV490 BE study, but 2 participants withdrew after randomisation before they received a dose of Xromi. Overall, 28 subjects received Xromi.

[b]Out of 33 subjects who were enrolled in the INV543 HUPK trail, 1 subject withdrew prior to receiving a dose of Xromi. Overall 32 subjects received Xromi.

**Table 4 Estimated Subject Exposure to Xromi Oral Solution by Demographic Variable**

| Age Range | Number of Subjects | | |
|---|---|---|---|
| | Male | Female | Total |
| **Bioequivalence trial (RD 729/26118) (INV490 BE)** | | | |
| 21-50 years | 24 | 4 | 28 |
| **Paediatric trial (INV543)** | | | |
| < 2 years | 1 | 5 | 6 |
| 2-5.99 years | 11 | 5 | 16 |
| 6-17.99 years | 4 | 6 | 10 |
| **Total** | **40** | **20** | **60** |

**Table 5 Estimated Subject Exposure to Xromi Oral Solution by Race**

| Racial Group | Number of Subjects |
|---|---|
| **Bioequivalence trial (RD 729/26118) (INV490 BE)** | |
| Caucasian | 28 |
| **Paediatric trial (INV543)** | |
| Black or African American | 30 |
| Caribbean [sic] (*self-described)* | 1 |
| Black British *(self-described)* | 1 |
| **Total** | **60** |

# MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Active substance(s): Hydroxycarbamide

Product(s) concerned: Xromi 100 mg/mL oral solution

MAH name: Lipomed GmbH.

Data lock point for this module: 16 Apr 2019

RMP version number when this module was last updated: 1.0

## SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Not applicable.

## SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Not applicable.

## SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Not applicable.

## MODULE SV POST-AUTHORISATION EXPERIENCE

Active substance(s): Hydroxycarbamide

Product(s) concerned: Xromi 100 mg/mL oral solution

MAH name: Lipomed GmbH.

Data lock point for this module: 30-Aug-2023

RMP version number when this module was last updated: 4.3

### SV.1 Post-authorisation Exposure

Xromi was first authorised in EU and EEA (Iceland, Norway and Lichtenstein) by the centralised procedure on 01 July 2019. Xromi is now approved in the Great Britain independently of the EU. Xromi 100 mg/mL oral solution is currently indicated for the prevention of vaso-occlusive complications of SCD in patients >2 years of age and this indication has been extended to patients > 9 months. From the estimated number of bottles of Xromi oral solution sold, the cumulative exposure post authorization of Xromi was estimated to be between 56,689 and 113,378 patient-months or between 4,724 and 9,448 patient-years. Although limited data suggest that 20mg/kg/day reduced painful episodes and were safe in children less than 2 years of age, safety of long-term treatment remains to be established. No exposure is available on the use of Xromi in other oncology indications.

The role of hydroxycarbamide in the treatment and disease modification of sickle cell has been established over almost 30 years through a number of randomised controlled trials and observational studies. Hydroxycarbamide is a well-established product with a known safety profile.

## MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Active substance(s): Hydroxycarbamide

Product(s) concerned: Xromi 100 mg/mL oral solution

MAH name: Lipomed GmbH.

Data lock point for this module: 16 Apr 2019

RMP version number when this module was last updated: 1.0

### Potential for Misuse for Illegal Purposes

Not applicable.

# MODULE SVII IDENTIFIED AND POTENTIAL RISKS

Active substance(s): Hydroxycarbamide

Product(s) concerned: Xromi 100 mg/mL oral solution

MAH name: Lipomed GmbH.

Data lock point for this module: 30-Aug-2023

RMP version number when this module was last updated: 4.3

## SVII.1 Identification of Safety Concerns in the Initial RMP Submission

### SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

**Reason for not including an identified or potential risk in the list of safety concerns in the RMP:**

**Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):**

- Gastrointestinal disorders
- Generalised skin reactions (Oral, ungal and cutaneous pigmentation, rash melanonychia, alopecia, cutaneous dryness)

Gastrointestinal disorders and skin and subcutaneous tissue disorders have been known to occur commonly in patients receiving hydroxycarbamide. Gastrointestinal disorders and skin reaction like oral, ungal and cutaneous pigmentation, rash, melanonychia, alopecia and cutaneous dryness are generally mild to moderate in intensity, and reversible upon discontinuation. Mostly they do not impact on the patient's quality of life and have minimal clinical impact. Acute mucocutaneous toxicity has been reported with Hydroxycarbamide several times above therapeutic doses in the form of soreness, violet erythema, oedema on palms and soles leading to scaling of hand and feet, severe generalised hyperpigmentation of the skin and stomatitis. There are reports of more severe forms of skin reactions like leg ulcers and vasculitis, panniculitis with long term use of hydroxycarbamide (Mattessich et al., 2017, Sirieix et al., 1999, Burgstallar et al., 2018), which are discussed in detail under important potential risk.

**Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:**

None.

**Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each European Union (EU) Member state where the product is authorised):**

- Macrocytosis

Macrocytosis is a very common manifestation of hydroxycarbamide therapy in oncology and non-oncology indications as well (Spier et al., 1971). Hydroxycarbamide induced macrocytosis is not B12 and folic acid dependent instead it is volumetric erythrocytosis (Burns et al., 1986).

The Xromi Summary of Product Characteristics (SmPC) does specify this in Section 4.4 and Section 4.8 and it is advised to use folic acid prophylactically during hydroxycarbamide treatment as macrocytosis caused by it may mask the incidental development of folic acid and vitamin B12 deficiency.

**Known risks that do not impact the risk-benefit profile:**

None

**Other reasons for considering the risks not important:**

None

### SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

**Important Identified Risk 1: Effects on male fertility – Oligospermia and azoospermia with normal morphology and reduced semen volume.**

Risk-benefit impact: Low, as it is reversible with discontinuation of hydroxycarbamide and the option of cryopreservation is available.

Effects on fertility are known to be generally reversible. Male fertility issues such as delayed puberty, sperm abnormalities and low testosterone level could be directly linked to the underlying sickle cell disease (SCD). Intensification with hydroxycarbamide during childhood might change these related-disease events however hydroxycarbamide is itself deleterious for the sperm cells. There are reports of significant reduction of spermatogonial quantity or total depletion in testes in pre-pubertal boys treated with hydroxycarbamide in SCD which was reversible on discontinuation of hydroxycarbamide. Also the exposure to previous cytotoxic agents; specifically alkylating agents need to be taken into consideration before starting on potentially sterilizing oncological treatments and fertility preservations (Stukenborg et al, 2018). Cryopreservation may be very useful if the resolution of hydroxycarbamide-induced lesions is prolonged and if the patient wishes to become a father (Habibi et al., 2017). Sahoo et al (2017) reported on a prospective study of the effect of hydroxycarbamide on seminal fluid

parameters in 100 male SCD patients, aged 15 to 45 years. The investigators found that alteration of sperm parameters is seen in a significant number of SCD patients, and is further exacerbated by hydroxycarbamide treatment even at low doses.

Effect on male fertility is also supported by the studies done in animals as below:

Hydroxycarbamide administered to male rats at 60 mg/kg by weight (b.w.)/day (about double the recommended usual maximum dose in humans) produced testicular atrophy, decreased spermatogenesis and significantly reduced their ability to impregnate females.

Doses of hydroxycarbamide in mice at 50 mg/kg orally or 100 mg/kg intraperitoneal correlate with 25 mg/kg oral doses in humans. These doses of hydroxycarbamide in mice increase testicular germ cell apoptosis induced testicular atrophy, decrease sperm count, decrease sperm motility, and increase abnormal sperm morphology. A study using sickle cell transgenic mice demonstrated that these mice have hypogonadism at baseline. After treatment with hydroxycarbamide at 25 mg/kg/day these mice exhibited decreased testicular size and increased sperm abnormalities compared with controls (Smith-Whitley 2014).

Based on findings in animals and humans, male fertility may be compromised by treatment with hydroxycarbamide. Therefore it is proposed to add wording to Section 4.6 (Fertility, pregnancy and lactation), and Section 4.8 (Undesirable Effects) of the SmPC, with the following wording:

*Fertility in males might be affected by treatment. Very common reversible oligo and azoospermia have been observed in men, although these disorders are also associated with the underlying disease.*

*Male patients should be informed by their healthcare professionals about the possibility of sperm conservation (cryopreservation) before the start of therapy.*

Wording for the Xromi package leaflet (PL):

*Xromi may decrease sperm production and cause fertility problems in male patients while they are being treated. Talk to your doctor or nurse if this is a concern for you.*

There is little known about the effect on female fertility with hydroxycarbamide use. Menses onset is delayed in females with SCD, but menstrual bleeding patterns are normal (Luban et al., 1982 and Zemel et al., 2007).

Whilst women with SCD have disease related factors that can impact their ability to conceive, including chronic inflammation, oxidative stress, transfusion-related hemochromatosis, and ovarian sickling, causing ischaemia and reperfusion injury to the ovary, there is no evidence that hydroxycarbamide affects their ability to conceive.

However, as already acknowledged, hydroxycarbamide may be teratogenic and hence should be avoided during pregnancy. Appropriate warnings and precautions are included in Section 4.6 (Fertility, pregnancy and lactation) of the SmPC.

Risks will be managed via routine pharmacovigilance activities.

Additional risk minimization will be undertaken by communicating this risk to physicians/healthcare providers and patients, using educational materials.

**Important Identified Risk 2: Myelosuppression**

Important Identified Risk 2: Myelosuppression

Risk-benefit impact: Low as risk is well documented and reversible upon discontinuation.

Cytotoxicity with neutropenia is the first and most common manifestation of haematological suppression, while thrombocytopenia/anaemia occurs less frequently and is rarely seen without a preceding neutropenia. Recovery from myelosuppression is usually rapid when therapy is discontinued. Treatment can then be re-initiated at a lower dose.

Refer to Section 4.2 (Posology and method of administration) of the Xromi 100 mg/mL oral solution SmPC, where clear instructions are given to healthcare providers for haematological monitoring and dose titration.

The ESCORT-HU interim data, recently reported at the 12th Annual Symposium of the FSCDR (Federation of SCD Research) 15 Jun 2018, confirm that HU is an efficient and well tolerated drug in both children and adults.

The ESCORT-HU study - at the last data analysis cut off point of June 2017, 1,921 patients had been enrolled. Patients have come from 63 centres in France, Germany, Greece, and Italy. Of the 1,829 patients with data available for analysis, 804 were under the age of 18. The paediatric patients were a mean 9 years of age, and the adult patients were a mean 33 years old at enrolment. Most enrolees (84%) have the HbSS genotype. Data collection for the study will end in 2018, with safety and efficacy data are expected in 2019.

Overdose is expected with Xromi, as is expected with any other medicinal product.

There are reports of neutropenia with Sickle Cell Syndrome in isolated cases of hydroxycarbamide overdose (1.43 times to 8.57 times of the maximum recommended dose of 35 mg/kg body weight/ day). But the evidence supports that with supportive care alone, full and spontaneous recovery of bone marrow function is possible in adult hydroxycarbamide overdose. There is no known antidote for Xromi. Overdose should be managed by close monitoring of blood counts and general supportive measures, together with appropriate blood transfusion, instituted if necessary. Treatment of overdose consists of gastric lavage, followed by symptomatic treatment and control of bone marrow function. Active measures (such as the use of activated charcoal or gastric lavage) may not be effective in the event of Xromi overdose unless the procedure can be undertaken within 60 minutes of ingestion.

It is recommended that blood counts are monitored for several weeks after overdose since recovery may be delayed and Xromi SmPC clearly specifies this (Miller et al., 2012 and Litt et al., 2013).

Risks will be managed via routine pharmacovigilance activities.

Considering the potential risk of medication error with the availability of 2 syringe sizes in the product packaging, and the expected off label use in children below 2 years, in whom there is a potentially increased risk of inadvertent overdose. Reports of overdoses and associated myelosuppressive/ any other events will be monitored closely and will be reported in detail in upcoming PSURs.

Additional risk minimization will be undertaken by highlighting this risk via physician and patient educational materials.

**Important Potential Risk 1: Mutagenicity and Carcinogenicity – Secondary cancers (e.g., Leukaemias)**

Risk-benefit impact: Low, as per the ESCORT- HU interim results (12th Annual Symposium of the FSCDR 15 Jun 2018) - no secondary cancers have been reported in this cohort to date. It should also be considered that the life expectancy of SCD patients is shorter.

In patients receiving long-term hydroxycarbamide for myeloproliferative disorders, secondary leukaemia has been reported. It is unknown whether this leukaemogenic effect is secondary to hydroxycarbamide, or whether it is associated with the patient's underlying disease.

A prospective analysis concluded that the sequential use of busulphan and hydroxycarbamide in essential thrombocythemia patients significantly increased the risk of second malignancies; and overall survival was not affected by hydroxycarbamide therapy. It was recommended not to use hydroxycarbamide in patients at low thrombotic risk and those who are already treated with cytotoxic agents (Finazzi et al., 2000).

Also, with the increase in the life expectancy of the SCD patients due to improved treatment and care, there is a 72% increase in haematological cancers and a 38% reduction in risk for solid cell cancers (Brunson et al., 2017), which is unrelated to hydroxycarbamide use. To lower the risk of increase in haematological cancers, screening of common cancers is suggested.

Per ESCORT- HU interim results (12th Annual Symposium of the FSCDR 15 Jun 2018), no secondary cancers have been reported in this prospective cohort to date. Additional information on frequency of malignancies is expected with the final results of the ESCORT-HU study.

Section 4.4 of the Xromi 100 mg/mL oral solution SmPC describes that the use of long-term hydroxycarbamide is associated with increased secondary leukaemias when used in myeloproliferative disorders. Section 4.2 of the SmPC makes it clear that use of Xromi 100 mg/mL oral solution requires close clinical monitoring. The haematological status of the patient should be determined prior to, and repeatedly during treatment.

In addition, cases of skin cancer have also been reported in patients receiving long-term hydroxycarbamide. Development of non-melanoma skin cancer is a well described risk of hydroxycarbamide. It most often occurs on sun-exposed areas of the skin, in patients with Fitzpatrick skin types I and II and in older patients with higher cumulative exposures to UV radiation. Recurrence and skin cancers have been observed to develop several years after

discontinuation of hydroxycarbamide therapy, necessitating long term surveillance. Section 4.4 of the SmPC will be updated to include relevant information to minimise the risk of skin cancer.

Risks will be managed via routine pharmacovigilance activities.

Additional risk minimization will be undertaken by highlighting this risk via physician and patient educational materials.

**Important Potential Risk 2: Off-label use in the oncology indications not approved for this formulation (with capsule formulation)**

Risk-benefit impact: Low, as Xromi 100 mg/mL oral solution will be available only with prescription and will limit the off-label use of the product. Educational materials will also be provided to prescribers.

Xromi 100 mg/mL oral solution, is an oral solution. An oral solution will always have the potential benefits for use in children and patients with dysphagia. But with this potential benefit there are more chances that the solution will be used off-label for children or patients with dysphagia for other unapproved indications e.g. haematological malignancies..

Section 4.1 (Therapeutic indication) of the Xromi 100 mg/mL oral solution SmPC provides clear guidance to avoid potential off-label use. As Xromi 100 mg/mL oral solution will be available as use only with prescription; there will always be oversight by the specialist or haematologist who will have oversight on potential off-label use expected for this product.

Risks will be managed via routine pharmacovigilance activities and off-label use cases will be documented in periodic safety update reports (PSURs).

**Important Potential Risk 3: Off-label use for chronic severe anaemia/thalassemia, polycythaemia**

Risk-benefit impact: Low, as Xromi 100 mg/mL will be available only with prescription and educational materials for healthcare prescribers, and will limit the off-label use of the product.

Hydroxycarbamide is licensed for vaso-occlusive crises in SCD in the EU. However based on United States and European expert panel recommendations (Yawn et al., 2014, Rakotoson et al., 2015) and results from placebo-controlled clinical trials, hydroxycarbamide could be useful in SCD patients with severe anaemia without vaso-occlusive crises since it has been demonstrated to increase total haemoglobin level (Wang 2011) and to decrease the need for blood transfusion. Though the haemoglobin increases, safety is not different from the non-anaemic population. Regular blood counts should also be part of the routine medical management and follow-up and managed accordingly (De Montalembert et al., 2017). With this evidence of beneficial effect in severe chronic anaemia with the same safety profile as of non-anaemic population, there will be increased chance of off-label use for severe chronic anaemia.

The results of a prospective long-term study of hydroxycarbamide in polycythaemia vera patients showed that there was adequate control of red cells, platelets, and spleen size. Cytopenia was not observed. Phlebotomy requirements were markedly reduced. Leukocyte alkaline phosphatase scores were generally lowered and several blood chemistry values returned to normal with minimal side effects (West, 1987). The beneficial effect of hydroxycarbamide in polycythaemia Vera has been demonstrated in many studies over time. Hence, the possibility of off-label use of Xromi 100 mg/mL oral solution cannot be denied.

Zamani F et al. (2009) evaluated the long-term efficacy and safety of hydroxycarbamide in major β-thalassemic patients. They observed a substantial and persistent increase in haemoglobin level and a significant decrease in blood transfusion. Hydroxycarbamide treatment was well-tolerated and did not cause any haematopoietic suppression except in one patient who developed transient thrombocytopenia which resolved after a short period of hydroxycarbamide cessation. No malignancies including leukaemia were encountered in the five-year follow-up. With these data available the chance of off-label use of Xromi 100 mg/mL oral solution cannot be denied.

Section 4.1 (Therapeutic indication) of the Xromi 100 mg/mL oral solution SmPC provides clear guidance to avoid potential off-label use. As Xromi 100 mg/mL oral solution will be available only on prescription; there will always be oversight by the specialist or haematologist which will have a check on potential off- label use.

Risks will be managed via routine pharmacovigilance activities and off-label use cases will be documented in PSURs.

**Important Potential Risk 4: Potential medication errors – Transfer of patients from capsule and tablet to liquid formulation and two dosing syringes.**

Risk-benefit impact: Low, as the SmPC and PIL for Xromi 100 mg/mL specify the method of administration and will help to keep this risk under control.

With an approved oral capsule and tablet formulations available on the market, there is a chance of conversion of patients from oral capsule/tablet to oral solution. Also Xromi 100mg/ mL administration is accompanied with two syringes. With conversion there is possibility of an impact on dose though Xromi 100 mg/mL oral solution is considered bioequivalent and therefore interchangeable as per the data available from the bioequivalence study. There is also a risk of potential medication error with use of two syringes for dose calculation and administration.

Xromi 100 mg/mL oral solution SmPC and PIL provides clear instructions in Section 4.2 (Posology and method of administration), PIL, Section 3 ‘How to take Xromi to avoid the potential for medication error. As Xromi 100 mg/mL oral solution will be available only on prescription and doses in SCD are titrated (individualised) according to the patients neutrophil and platelet count, there will always be oversight by the specialist or haematologist.

Risks will be managed via routine pharmacovigilance activities including signal detection and medication error cases will be reviewed in PSURs.

Additional risk minimization will be undertaken by highlighting this risk to physicians and patients via educational materials.

**Important Potential Risk 5: Skin ulceration and vasculitis**

Risk-benefit impact: Low – considering the benefits of treatment and that the effect is reversible upon discontinuation of treatment. Successful therapies are also now available for management of leg ulcers/vasculitis (Stagno et al., 1999 and Mattessich et al., 2017).

Hydroxycarbamide is usually well tolerated; however, long-term hydroxycarbamide therapy has been associated with cutaneous side effects, such as alopecia, diffuse hyperpigmentation, erythema, skin atrophy, and nail changes. Painful skin ulcers have been also reported and their treatment modalities mainly consisted of hydroxycarbamide discontinuation, which was generally followed by the complete or almost complete healing (Mattessich et al., 2017 and Sirieix et al., 1999)

There are reports of cutaneous ulcers from a large retrospective study complicating the treatment with hydroxycarbamide for myeloproliferative neoplasm. Complete wound healing was seen after stopping hydroxycarbamide, after a mean period of 5 months (Burgstaller et al., 2018).

There have been reports of leg ulcers with avascular necrosis of the femoral head while treated with hydroxycarbamide for SCD (Warang et al., 2018).

It has been demonstrated that hydroxycarbamide is known to have skin ulceration not only when indicated for SCD but also other indications.

Risks will be managed via routine pharmacovigilance activities.

Additional risk minimization will be undertaken by highlighting this risk via physician and patient educational materials.

**Important Potential Risk 6: Off-label use in children < 2years old**

Risk-benefit impact: Low, as Xromi 100 mg/mL will be available on prescription only and will limit the off-label use of the product.

Xromi is an oral solution which will facilitate dose administration in children below 2years of age. The ease of administration increases the chances of it being used off –label not only for SCD but also for other approved and unapproved indications of hydroxycarbamide.

Xromi 100 mg/mL oral solution SmPC provides clear instructions that it is indicated in children above 2 years of age.

The potential for medication errors as a consequence of incorrect use of oral syringe may increase the risk of overdose in children below the age of 2 years.

Risks will be managed via routine pharmacovigilance activities and off-label use cases will be documented in PSURs. Also, the reports of overdose and associated myelosuppressive/ any other events will be monitored closely and will be reported in detail in PSURs.

Additional risk minimization will be undertaken by highlighting this risk via physician and patient educational materials

**Important Potential Risk 7: Concurrent use of hydroxycarbamide with nucleoside analogue reverse transcriptase inhibitors and other myelosuppressive medicinal products or radiation therapy**

Risk-benefit impact: Low, the expected adverse drug reactions (ADRs) due to drug interaction are reversible upon drug discontinuation. In addition the frequency of these interactions is rare.

Potentially fatal pancreatitis and hepatotoxicity and severe peripheral neuropathy have been reported in HIV virus patients who received hydroxycarbamide in combination with antiretroviral drugs, particularly didanosine plus stavudine. Median decline in CD4 cells of approximately 100/mm$^3$ is also reported with concomitant use. (Bloch et al., 2016, Havlir et al., 2001, Rutschmann et al., 1998, Rutschmann et al., 2000, and Swindells et al., 2005)

Also concurrent use of hydroxycarbamide and other myelosupressive products or radiation therapy may increase bone marrow depression, gastrointestinal disturbance and mucositis. Erythema caused by radiation maybe aggravated by hydroxycarbamide.

Cutaneous vasculitis toxicities including ulcerations and gangrene is more reported in patient with myeloproliferative disorder if hydroxycarbamide is used concomitantly with interferon therapy or used in patient with prior exposure to interferon therapy.

These interactions are described in detail in Xromi SmPC Section 4.5.

Risks will be managed via routine pharmacovigilance activities.

Additional risk minimization will be undertaken by highlighting this risk via physician and patient educational materials.

**Important Potential Risk 8: Interaction with live bacterial or virus vaccines**

Risk-benefit impact: Low, as Xromi 100 mg/mL is available with on prescription only and prescribing physicians and dispensing pharmacist will be made aware about interaction of this product with live virus vaccine.

Concomitant use of hydroxycarbamide with a live virus vaccine may potentiate the replication of the vaccine virus and/or increase the adverse drug reaction of the vaccine virus, because normal defence mechanism may be suppressed by hydroxycarbamide therapy. It may result in severe infections. Generally, patient's antibody response to vaccines may be decreased.

Xromi 100 mg/mL oral solution SmPC provides clear instructions in Section 4.5 that, Xromi and concomitant immunisation with live virus vaccines should only be performed if benefits clearly outweigh potential risks.

Risks will be managed via routine pharmacovigilance activities.

**Important Potential Risk 9: The effect on embryogenesis, teratogenic potential, breastfeeding and post-natal development**

Risk-benefit impact: Low, as Xromi 100 mg/mL is available on prescription only and prescribing physicians and dispensing pharmacist will be made aware about contraindication of the product in pregnancy or avoiding pregnancy while receiving this product via SmPC and educational materials will be provided to healthcare prescribers.

Some teratogenic effects of hydroxycarbamide have been observed in foetuses of treated pregnant rodents (Woo et al., 2004; Yan and Hales 2005; Chahoud and Paumgartten 2009). Hydroxycarbamide has been demonstrated to be embryotoxic at doses over 150 mg/kg/day in rats and in monkeys (Liebelt et al., 2007). Embryotoxicity was characterised by decreased foetal viability, reduced live litter sizes, and developmental delays. In contrast, a recent study on pregnant mice showed no evidence of teratogenic effects with intraperitoneal injection of hydroxycarbamide (25 mg/kg) on gestation day 7.5 (Guan et al. 2015 and Joseph et al., 2016).

The National Toxicology Program (NTP) found that hydroxycarbamide can cross the placenta and is found in breast milk and as such use of hydroxycarbamide in pregnancy/lactation could lead to exposure to the unborn child and infant (NTP, 2008).

With the evidence of pre-clinical teratogenic effect and the evidence that hydroxycarbamide can cross the placenta, Xromi 100 mg/mL oral solution is contraindicated during pregnancy and breastfeeding/lactation as indicated in Section 4.3 and Section 4.6 of the SmPC.

Risks will be managed via routine pharmacovigilance activities.

Additional risk minimization will be undertaken by highlighting this risk via physician and patient educational materials.

**Important Potential Risk 10: Safety of hydroxycarbamide in patients with underlying hepatic or renal impairment**

Risk-benefit impact: Low, patients can be monitored regularly for the renal and hepatic parameters before start of the therapy and throughout therapy. Xromi can be discontinued if required and re-started on lower dose.

There are no data that support specific guidance for dose adjustment in patients with hepatic impairment, but due to safety considerations (considering the hepatic elimination), Xromi 100 mg/mL oral solution is contraindicated in patients with severe hepatic impairment (Child-Pugh Classification C) and a warning is included in Section 4.3 (Contraindications) of Xromi 100 mg/mL oral solution SmPC.

In Section 5.2 of the Xromi 100 mg/mL oral solution SmPC it is advised to closely monitor blood parameters in patients with hepatic impairment.

Blood parameters for renal and hepatic impairment should be closely monitored, and Xromi should be discontinued if necessary. If appropriate, Xromi should be re-started at a lower dose.

As renal excretion is a main pathway of elimination, dose reduction of Xromi 100 mg/mL oral solution should be considered in patients with renal impairment. In patients with a creatinine clearance ≤ 60 mL/min the initial Xromi dose should be decreased by 50%. Guidance on the dosage of Xromi 100 mg/mL oral solution in patients with renal impairment is included in Section 4.2 of the SmPC.

Xromi 100 mg/mL oral solution is contraindicated in patients with severe renal impairment (<30 mL/min) and a warning is included in Section 4.3 (Contraindications) of the Xromi SmPC.

In Section 5.2 of the Xromi 100 mg/mL oral solution SmPC it is advised to closely monitor the blood parameters in these patients.

Risks will be managed via routine pharmacovigilance activities.

Additional risk minimization will be undertaken by highlighting this risk via physician and patient educational materials.

**Important Potential Risk 11: Systemic and Cutaneous Lupus erythematosus**

Risk-benefit impact: Low, given the positive effects of hydroxycarbamide treatment for SCD, the condition is also reversible on dose reduction or discontinuation of hydroxycarbamide.

Hydroxycarbamide dermopathy is a unique dermatomyositis-like eruption occurring in patients after an average of 5 years of hydroxycarbamide therapy. A prior study of the immunologic effects of hydroxycarbamide has demonstrated high anti-double-stranded deoxyribonucleic acid (DNA) levels. Previous cases of hydroxycarbamide dermopathy have generally not displayed any notable serologic markers. Hydroxycarbamide induced lupus erythematous is a rare entity, but there are reports of both cutaneous and systemic lupus erythematous cases in literature, the diagnosis of which were supported by biopsy results and relationship was established with recovery or improvement in these cases on discontinuation of hydroxycarbamide (Yanes and Mosser-Goldfarb, 2017, Layton and Cotterill, 1994, Mebazaa et al. 2009).

After considering the evidence from MAH's of hydroxycarbamide, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended that MAHs of hydroxycarbamide-containing products should submit a variation within 2 months to amend the product information.

As per this recommendation from PRAC, Xromi SmPC has been updated to include "Systemic and Cutaneous Lupus Erythematous" in Section 4.8 as very rare adverse drug reaction and PL paragraph 4 will need to be updated to include the wording "Possible side effects: Inflammation of the skin causing red scaly patches and possibly occurring together with pain in the joints".

Risks will be managed via routine pharmacovigilance activities.

**Missing Information 1: Influence of hydroxycarbamide in child and adolescent growth (end of puberty)**

Risk-benefit impact: Low – unknown Poor nutritional status and growth, academic failure and delayed puberty are some of the symptoms of paediatric SCD. As per the interim results of the HUSOFT (Hydroxyurea Safety and Organ Toxicity) study, children started on hydroxycarbamide for the long-term had normal growth and development, are in school at appropriate grade level, and continue to experience very few vaso-occlusive episodes and minimal blood utilisation. This is the first cohort of children to be reported who have had hydroxycarbamide therapy continuously prescribed for this length of time (15 years approximately).

It is anticipated that the final, long-term study results from BABY HUG (a Phase III double-blinded, multi-centre, randomised, placebo- controlled infant hydroxycarbamide study) and ESCORT-HU (European Sickle Cell Disease Cohort-Hydroxyurea) study final results are expected in 2019. Upon receipt of this data, RMP will be updated accordingly.

Management of paediatric patients with SCD should include acute care, routine prevention (e.g. childhood vaccinations and monitoring of growth and development), and the treatment of complications (e.g. cardiac, respiratory, and renal). Careful attention should be paid to the academic achievement of children with SCD in order to screen for possible silent infarct, which would warrant magnetic resonance imaging evaluation.

Long-term safety effects in children will be monitored through routine pharmacovigilance activities and reported in PSURs. Also, Section 4.4 (Special warnings and precautions for use) of the Xromi 100 mg/mL oral solution SmPC contains a recommendation that continuous follow-up of the growth of treated children and adolescents is recommended.

## SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

As per previous regulatory request received from PRAC as part of PSUR assessment report for the period of 01-Jul-2019 to 28-July-2020 (EMEA/H/C/PSUSA/00001692/202006) below updates were done to the risks and missing information of Xromi and were approved via EMEA/H/C/004837/IB/0012 resulting from PSUSA/00001692/202006 as part as currently effective RMP version 4.0:

- Interstitial lung disease in the SCD population is a new important potential risk.
- Hyperkalaemia in the SCD population is a new important potential risk.
- Hyponatremia in the SCD population is a new important potential risk.

- Myelosuppression previously classified as important identified risk is removed from the list of safety concerns.
- Concurrent use of hydroxycarbamide with nucleoside analogue reverse transcriptase inhibitors and other myelosuppressive medicinal products or radiation therapy previously classified as important potential risk is to be reclassified as missing information.
- Interaction with live bacterial and virus vaccines previously classified as important potential risk is to be reclassified as missing information.
- Influence of hydroxycarbamide in child and adolescent growth (end of puberty) previously classified as missing information is removed from the list of safety concerns.

The MAH has submitted the RMP version 4.3 due to the request of extension of paediatric indication via EMEA/H/C/004837/II/0019 and the following updates were performed as per Regulatory Requests included in the Assessment Report.

- Interstitial lung disease in the SCD population previously classified as important potential risk is removed from the list of safety concerns.
- Hyperkalaemia in the SCD population previously classified as important potential risk is removed from the list of safety concerns.
- Hyponatremia in the SCD population previously classified as important potential risk is removed from the list of safety concerns.
- Concurrent use of hydroxycarbamide with nucleoside analogue reverse transcriptase inhibitors and other myelosuppressive medicinal products or radiation therapy previously classified as missing information is removed from the list of safety concerns.
- Interaction with live bacterial and virus vaccines previously classified as missing information is removed from the list of safety concerns.
- Mutagenicity and Carcinogenicity – Secondary cancers (e.g., Leukaemias) previously classified as important potential risk is removed from the list of safety concerns.
- Off-label use in the oncology indications not approved for this formulation (with tablet/capsule formulation) previously classified as important potential risk is removed from the list of safety concerns.
- Off-label use for chronic severe anaemia/thalassemia, polycythaemia previously classified as important potential risk is removed from the list of safety concerns.
- Skin ulceration and vasculitis previously classified as important potential risk is removed from the list of safety concerns.
- Safety of hydroxycarbamide in patients with underlying hepatic or renal impairment previously classified as an important potential risk.
- Systemic and Cutaneous Lupus erythematosus previously classified as an important potential risk.

- Off label use in children < 2 years old previously classified as important potential risk is removed from the list of safety concerns.
- Long-term safety in children below 2 years of age is a new missing information.

## SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

### SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Details of Important Identified Risks and Potential Identified Risks are presented in Table 6.

**Table 6 Details of Important Identified and Potential Risks**

| **Important Identified Risk #1** | |
|---|---|
| **Risk: Effects on male fertility – Oligospermia and azoospermia with normal morphology and reduced semen volume** | |
| Potential Mechanisms | Alteration of sperm parameters leading to Oligospermia and azoospermia, abnormal sperm production, alteration of seminal fluid parameters, testicular atrophy with decreased spermatogenesis and spermatogenic arrest, significantly reducing the ability to impregnate females. |
| Evidence Source and strength of evidence: | Berthaut et al., 2017,<br>Habibi et al., 2017,<br>Luban et al., 1982,<br>Smith-Whitley 2014,<br>Zemel et al., 2007,<br>Stukenborg et al., 2018,<br>Sahoo et al., 2017. |

| | |
|---|---|
| Characterisation of the risk | Hydroxycarbamide administered to male rats at 60 mg/kg bodyweight/day (about double the recommended usual maximum dose in humans) produced testicular atrophy, decreased spermatogenesis and significantly reduced their ability to impregnate females.<br>Hydroxycarbamide in mice increases testicular germ cell apoptosis induced testicular atrophy, decrease sperm count, decrease sperm motility, and increase abnormal sperm morphology at a dose of 50 mg/kg/body weight. A study using sickle cell transgenic mice demonstrated that these mice have hypogonadism at baseline. After treatment with hydroxycarbamide at 25 mg/kg/d these mice exhibited decreased testicular size and increased sperm abnormalities compared with controls.<br>Fertility in males might be affected with hydroxycarbamide treatment. Very common generally reversible oligo- and azoospermia have been observed in man, although these disorders are also associated with the underlying disease.<br>There are reports of significant reduction of spermatogonial quantity or total depletion in testes in pre-pubertal boys treated with hydroxycarbamide in SCD which was reversible on discontinuation of hydroxycarbamide.<br>This will be additive to the effect of underlying SCD on fertility.<br>There is little known about the effect on female fertility with hydroxycarbamide use. Menses onset is delayed in females with SCD, but menstrual bleeding patterns are normal.<br>Whilst women with SCD have disease related factors that can impact their ability to conceive, including chronic inflammation, oxidative stress, transfusion-related hemochromatosis, and ovarian sickling, causing ischaemia and reperfusion injury to the ovary, there is no evidence that hydroxycarbamide affects their ability to conceive. |
| Risk Factors or Risk Groups | Male population probably with long-term use of Xromi 100 mg/mL oral solution in childhood and adolescent age group. |
| Preventability | Cryopreservation, before starting treatment with Xromi 100 mg/mL oral solution. Treating physician to keep male patients well informed of infertility, an option of cryopreservation and discontinuation of hydroxycarbamide if felt necessary by the treating physician.<br>Also the exposure to previous cytotoxic agents; specifically alkylating agents need to be taken into consideration before starting on potentially sterilizing oncological treatments and fertility preservations |
| Impact on the risk-benefit balance of the product | Low, as it is reversible upon discontinuation of hydroxycarbamide and option of cryopreservation available. |
| Public Health Impact | Low |
| **Important Potential Risk #1** | |
| **Risk: Potential medication errors – Transfer of patients from capsule and tablet to liquid formulation and two dosing syringes** | |
| Potential Mechanisms | Not applicable. |
| Evidence Source and strength of evidence: | Estepp et al. 2016<br>Bioequivalence study results |

| | |
|---|---|
| Characterisation of the risk | With the availability of an approved oral capsule and tablet formulation available, there is a chance of conversion of patients from oral capsule/tablet to oral solution. With conversion there is titration possibility of an impact on dose although Xromi 100 mg/mL oral solution is considered bioequivalent and therefore interchangeable as per the data available from the bioequivalence study. There is also a potential risk of medication error with the use of two syringes for dose calculation and administration. |
| Risk Factors or Risk Groups | Paediatric population and use in patients prescribed with capsule or tablet formulation. |
| Preventability | Supervision by the specialist and haematologist as prescription only use product and doses in SCD need to be titrated (individualised) according to the patients neutrophil and platelet count, will keep a check on medication errors as a consequence of converting from oral solution to capsule/tablet and vice versa. |
| Impact on the risk-benefit balance of the product | Low, as the SmPC and PIL for Xromi 100 mg/mL specify the method of administration and will help to keep this risk under control. |
| Public Health Impact | Low |
| **Important Potential Risk #2** | |
| **Risk: The effect on embryogenesis, teratogenic potential, breastfeeding and post-natal development** | |
| Potential Mechanisms | The principal and most well understood mechanism of action of hydroxycarbamide *in vivo* is the reversible inhibition of ribonucleotide reductase (RR), a critical enzyme that converts ribonucleosides into deoxyribonucleosides, which are required for the synthesis and repair of DNA.<br>Trans-species carcinogen, genotoxic, immediate inhibition of DNA synthesis, generation of nitric oxide leading to inhibition of DNA synthesis.<br>Xromi crosses placenta and is excreted in human milk. |
| Evidence Source and strength of evidence: | Chahoud and Paumgartten 2009,<br>Guan et al. 2015,<br>Joseph et al. 2016,<br>Liebelt et al. 2007,<br>Woo et al. 2004,<br>Yan and Hales 2005,<br>NTP 2008 |
| Characterisation of the risk | There is a known teratogenic effect of hydroxycarbamide in pre-clinical studies in the form of partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae. Embryotoxicity is characterized by decreased foetal viability, reduced live litter sizes and developmental delays. Therefore there is need to contraindicate the use of Xromi 100 mg/mL oral solution in pregnancy and during breastfeeding. |
| Risk Factors or Risk Groups | Pregnant and/or breastfeeding females, female of reproductive age group and foetus or children exposed to Xromi during pre-natal period. |
| Preventability | Contraindicating use of Xromi in pregnancy, educating patients to report pregnancy immediately to prescribing physician. Effective method of contraception for both male and female patients in reproductive age group. Discontinuation of Xromi 3 to 6 months before, if patient on treatment want to conceive. |

| | |
|---|---|
| Impact on the risk-benefit balance of the product | Low, as prescription only drug and SmPC provide sufficient information to prescribing physician about contraindication and discontinuation of Xromi in pregnancy, which will keep a check. |
| Public Health Impact | Low |

Abbreviations: DNA = deoxyribonucleic acid; PIL = patient information leaflet; SCD = Sickle cell disease; SmPC = Summary of Product Characteristics.

### SVII.3.2 Presentation of the Missing Information

Details of missing information are presented in Table 7.

**Table 7 Details of missing information**

| **Missing Information** | |
|---|---|
| **Missing information #1** | |
| **Long-term safety in children below 2 years of age** | |
| Evidence Source | There are limited data available to allow extrapolation of safety data to paediatric population of 9 months to 2 years of age. Safety data from the BABY HUG trial in children with SCD from 9 months to 18 months of age showed that, there were no adverse effects on growth or other anthropomorphic measures during 2 years of hydroxycarbamide therapy in fixed dose of 20 mg/kg/day. Data from the BABY-HUG study and the limited data from the PK study INV543, showed that the safety of hydroxyurea in children < 2 years of age appears to be in line with the known safety profile of the drug. However, the limited number of study participants in the age group of 9 months to 2 years of age made it difficult to draw definitive conclusions on the long-term safety of hydroxycarbamide in children below 2 years of age |
| Population in need of further characterisation | Patients with Sickle Cell Disease under 2 years of age |
| Anticipated risk/consequence of the missing information | Safety data from the BABY HUG trial in children with SCD from 9 months to 18 months of age showed that infants treated with hydroxycarbamide did not have significant differences from those treated with placebo in rates of severe neutropenia ANC, thrombocytopenia, anaemia (Hb), reticulocytopenia (ARC), or abnormal tests of liver function (alanine aminotransferase [ALT], bilirubin). However, BABY HUG was conducted in children from 9 months to 18 months of age and with fixed dose of 20mg/kg/day As the proposed maximum tolerated dose (MTD) is 35 mg/kg/day for the age group of 9 months to 2 years of age, dose escalation may cause increased toxicities, consistent with the known safety profile of hydroxycarbamide. In study INV543 a trend for higher frequency of AEs in the age group of 6 months to 2 years was observed; the majority of TEAEs were haematological toxicities. The temporary cessation and/or modification of dose led to resolution of symptoms and continuation in the study and did not require permanent withdrawal from the study drug. |

## MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Active substance(s): Hydroxycarbamide

Product(s) concerned: Xromi 100 mg/mL oral solution

MAH name: Lipomed GmbH.

Data lock point for this module: 29-Nov-2023

RMP version number when this module was last updated: 4.3

A Summary of safety concerns is presented in Table 8.

**Table 8 Summary of Safety Concerns**

| | |
|---|---|
| Important identified risks | 1. Effects on male fertility- Oligospermia and azoospermia with normal morphology and reduced semen volume |
| Important potential risks | 1. Potential medication errors – Transfer of patients from capsule and tablet to liquid formulation and two dosing syringes<br>2. The effect on embryogenesis, teratogenic potential, breastfeeding and post-natal development |
| Missing information | 1. Long-term safety in children below 2 years of age |

# PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

Active substance(s): Hydroxycarbamide

Product(s) concerned: Xromi 100 mg/mL oral solution

MAH name: Lipomed GmbH.

Data lock point for this module: 03-Sep-2025

RMP version number when this module was last updated: 7.0

## III.1 Routine Pharmacovigilance Activities

**Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:**

**Specific Adverse Reaction Follow-up Questionnaires**:

Lipomed GmbH will be using a standard pregnancy follow-up form/questionnaire to follow-up on cases of pregnancy/lactation

**Other Forms of Routine Pharmacovigilance Activities:**

Not applicable

## III.2 Additional Pharmacovigilance Activities

In a pre-Investigational New Drug Type C meeting with the Food and Drug Administration, the previous MAH Nova Laboratories Ltd. was advised to conduct a pharmacokinetics (PK) study in children aged 6 months up to 18 years, as support for a future New Drug Application. Scientific advice from the Committee for Medicinal Products for Human Use also suggested that PK data in infants less than 2 years of age is lacking.

the previous MAH Nova Laboratories conducted an open label, single arm, multi-center, PK, safety and efficacy study, involving sites in Jamaica and the United Kingdom (Paediatric Study INV543). The primary objective was to determine the PK of Xromi (hydroxycarbamide 100mg/ml oral solution). The secondary objectives were to determine the safety and tolerability and also to assess the effects of hydroxycarbamide on various laboratory and clinical parameters, along with its palatability and acceptability.

Overall, the PK profile of hydroxycarbamide in this study population aged from 6 months to 17.99 years was relatively uncomplicated with only weight being identified as an influential covariate. Hence, weight based dosing resulted in predictable, overlapping systemic exposure across the age groups. A robust HbF response to treatment was observed in all age groups.

All except one of the 32 study participants in the Safety Population experienced at least one Treatment Emergent Adverse Event (TEAE), which was expected given the serious and debilitating nature of SCA. There were 28 related TEAEs in 9 participants, the most frequent

of which were isolated and transient occurrences of haematological toxicity, which were typically associated with recent or concurrent illness (viral and upper respiratory tract infections). All SAEs and most of the Grade ≥3 AEs were considered unrelated to IMP and were indicative of the typical complications of SCA.

No study participants died during the study and only one study participant was discontinued permanently from IMP due to an unrelated AE (Principal investigator discretion to allow use of HU off-protocol). Laboratory results, vital signs and physical examination results were unremarkable except for isolated occurrences of haematological toxicity which were an expected result of dose titration.

Based on the study results, the previous MAH Nova proposed an extension of the indication for the prevention of vaso-occlusive complications of Sickle Cell Disease in children from 9 months of age.

Following the application for the extension of the indication, a *comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral solution 100 mg/ml) for the prevention of vaso-occlusive complications of Sickle Cell Disease in children under 2 years of age (PASS Study)* will be conducted.

**PASS of Xromi comparing safety and effectiveness in children under 2 years with Sickle cell disease summary**

Study short name and title:

PASS of Xromi comparing safety and effectiveness in children under 2 years with Sickle cell disease.

Comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral solution 100 mg/ml) for the prevention of vaso-occlusive complications of Sickle Cell Disease in children under 2 years of age.

Rationale and study objectives:

Rationale: As part of the extension of indication to include the prevention of vaso-occlusive complications of sickle cell disease in children from 9 months to 2 years of age for Xromi (variation II/0019), the authorities requested additional safety and efficacy data to further establish the risk benefit profile of hydroxycarbamide in children between the age of 9 months and 2 years.

The safety concern addressed is the Long-term safety in children below 2 years of age.

The main study objectives are summarised below:

- Primary Objective: Assessment of the incidence of adverse events of special interest (AESIs) in children who have SCD and are treated with hydroxycarbamide oral solution 100 mg/ml (Xromi), in comparison to a retrospective comparator cohort.

Secondary objective:

- Assessment of the effectiveness of Xromi for the clinical events and laboratory tests and physiological assessments of interest, in comparison to a retrospective comparator cohort.

Exploratory Objectives:

- To assess the overall safety of Xromi by describing AEs by severity, seriousness, relatedness, action taken, outcome, and duration.
- To describe occurrence of and reasons for discontinuation of Xromi.
- To assess the safety of Xromi at the optimised dose.
- To assess if the effectiveness of Xromi is associated with the dose.
- To assess the safety and effectiveness of Xromi by subgroups (age, sex, SCD subtypes, country).
- To assess occurrence of clinical events in comparators exposed to any formulation of hydroxycarbamide during follow-up.
- To assess organ function and potential preservation in children exposed to any formulation of hydroxycarbamide.

Study design:

Non-randomised, non-interventional, comparative, observational, hybrid prospective and retrospective, post-authorisation cohort study (a matched cohort design) of children with SCD from 9 months to under 2 years of age to assess the safety and effectiveness of Xromi based on primary and secondary data collection.

Study population:

The study population will consist of children aged from 9 months to under 2 years at the index date with SCD who meet all the inclusion criteria and none of the exclusion criteria according to the study protocol NOVDD-001. Identification of participants will be conducted as follows:

- Exposure cohort:
  - Prospective exposure: Potential participants will be identified as they attend the participating sites where eligibility criteria will be assessed.
- Comparator cohort:
  - Retrospective: Potential participants will be selected from clinical chart review.

Milestones:

Registration in the EU PAS register: March 2024

Start of study (first site Greenlight): 29 April 2025

Start of data collection (first patient enrolled): June 2025

End of data collection: June 2029

Interim progress reports: May 2026 and May 2028

Final Report of study results: June 2030

A summary of this study is presented in Table 9.

## III.3 Summary Table of Additional Pharmacovigilance Activities

### Table 9 Ongoing and Planned Additional Pharmacovigilance Studies

| 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 | | | | |
| NA | NA | NA | NA | NA |
| **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 | | | | |
| NA | NA | NA | NA | NA |
| **Category 3** - Required additional pharmacovigilance activities | | | | |

| | | | | |
|---|---|---|---|---|
| **Study: A comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral solution 100 mg/ml) for the prevention of vaso-occlusive complications of Sickle Cell Disease in children under 2 years of age (PASS Study).**<br><br>**Status: Planned** | **Primary objective:**<br>Assessment of the incidence of adverse events of special interest (AESIs) in children who have SCD and are treated with hydroxycarbamide oral solution 100 mg/ml (Xromi), in comparison to a retrospective comparator cohort.<br>**Secondary objective:**<br>• Assessment of the effectiveness of Xromi for the clinical events and laboratory tests and physiological assessments of interest, in comparison to a retrospective comparator cohort.<br>**Exploratory Objectives:**<br>• To assess the overall safety of Xromi by describing AEs by severity, seriousness, relatedness, action taken, outcome, and duration.<br>• To describe the occurrence of and reasons for discontinuation of Xromi.<br>• To assess the safety of Xromi at the optimised dose.<br>• To assess if the effectiveness of Xromi is associated with the dose.<br>• To assess the safety and effectiveness of Xromi by subgroups (age, sex, SCD subtypes, country).<br>• To assess occurrence of clinical events in comparators exposed to any formulation of hydroxycarbamide during follow-up.<br>• To assess organ function and potential preservation in children exposed to any formulation of hydroxycarbamide. | Long-term safety in children below 2 years of age. | Registration in the EU PAS register<br><br>Start of study<br><br>Start of data collection<br><br>End of data collection<br><br>Interim progress reports<br><br>Final report of study results | March 2024<br><br>April 2025<br><br>June 2025<br><br>June 2029<br><br>May 2026 and May 2028<br><br>June 2030 |

Abbreviations: NA = Not applicable; PASS = post authorisation safety study.

## PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Active substance(s): Hydroxycarbamide

Product(s) concerned: Xromi 100 mg/mL oral solution

MAH name: Lipomed GmbH.

Data lock point for this module: 16 Apr 2019

RMP version number when this module was last updated: 1.0

There are currently no post-authorisation efficacy studies ongoing or planned for Xromi 100 mg/mL oral solution.

# PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Active substance(s): Hydroxycarbamide

Product(s) concerned: Xromi 100 mg/mL oral solution

MAH name: Lipomed GmbH.

Data lock point for this module: 29- Feb-2024

RMP version number when this module was last updated: 5.0

## V.1 Routine Risk Minimisation Measures

The safety information in the proposed product information is aligned to the reference medicinal product and also on an evaluation of the literature reported studies of hydroxycarbamide in sickle cell disease (SCD). A description of routine risk minimisation measures by safety concern is presented in Table 10.

## Table 10 Description of Routine Risk Minimisation Measures by Safety Concern

| Safety Concern | Routine Risk Minimisation Measures |
|---|---|
| **Important Identified Risk** | |
| **Identified Risk #1** | |
| Effects on male fertility – Oligospermia and azoospermia with normal morphology and reduced semen volume | **Routine risk communication:**<br>The safety information in the proposed product information is aligned to the reference medicinal product and also on an evaluation of the literature reported studies of hydroxycarbamide in SCD.<br>Please refer to the following Sections of the Xromi 100 mg oral solution Summary of Product Characteristics (SmPC): Section 4.6 (Fertility, pregnancy and lactation) and Section 4.8 (Undesirable effects).<br>Please refer to the Section 2 of the Xromi 100 mg oral solution PL:<br>Pregnancy, breastfeeding and fertility:<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>Male patients should be informed by their healthcare professionals about the possibility of sperm conservation (cryopreservation) before the start of therapy. This recommendation has been added to Section 4.6 of the Xromi 100 mg oral solution SmPC and to Section 2 of the Xromi 100 mg/mL oral solution PL. |
| **Important Potential Risks** | |
| **Potential Risk #1** | |
| Potential medication errors – Transfer of patients from capsule and tablet to liquid formulation and two dosing syringes | **Routine risk communication:**<br>The safety information in the proposed product information is aligned to the reference medicinal product and also on an evaluation of the literature reported studies of hydroxycarbamide in SCD.<br>Please refer to the following Sections of the Xromi 100 mg oral solution SmPC: Section 4.2 (Posology and Method of Administration).<br>Please refer to Section 3 of the Xromi 100 mg oral solution PL where appropriate guidance is provided on taking the medicine along with instructional pictures:<br>How to take Xromi<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only medicinal product |

| **Potential Risk #2** | |
|---|---|
| The effect on embryogenesis, teratogenic potential, breastfeeding and post-natal development | **Routine risk communication:**<br>The safety information in the proposed product information is aligned to the reference medicinal product and also based on an evaluation of the literature reported studies of hydroxycarbamide in SCD.<br>Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC: Section 4.3 (Contraindications) and Section 4.6 (Fertility, pregnancy and lactation) and Section 2 of the PL.<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>The patient should be instructed to immediately contact a doctor in case of suspected pregnancy. Both male and female patients in reproductive age group should use effective methods of contraception before, during and after treatment with Xromi. The recommended duration of contraception in male and female patients following the end of treatment with Xromi should be 3 and 6 months, respectively. PL Section 2 instructions - Please contact your doctor immediately if you think you may be pregnant.<br>Please refer to Section 4.6 of SmPC and Section 2 of the Xromi 100 mg/mL oral solution PL where appropriate warnings are provided against use in pregnancy/lactation under "What you need to know before you take Xromi".<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only medicinal product. |
| **Important Missing Information** | |
| **Missing information #1** | |
| **Long-term safety in children below 2 years of age** | **Routine risk communication:**<br>Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC: Section 4.2 (Posology and method of administration) and Section 4.8 (Undesirable effects) and Section 2 of the PL. Please refer to Table 11 for additional pharmacovigilance activities undertaken to further characterize this missing information.<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only medicinal product |

Abbreviations: PL = Package leaflet; SCD = Sickle cell disease; SmPC = Summary of Product Characteristics

## V.2 Additional Risk Minimisation Measures

A separate educational material for physician and patient/parent will be prepared to communicate the important identified risks and important potential risk to the physician/healthcare professionals, patient/parent as a part of additional risk minimisation activities.

**Physician and Patient/ Parent guide: Educational leaflet**

**Objectives:**

To adapt prescribing behaviour, to ensure the safe and effective use of product, to minimise the risks listed below and to reduce the burden of adverse reactions with Xromi.

**List of key elements to be addressed:**

1. Need for contraception
2. Risk to male and female fertility, potential risk to foetus and breast feeding
3. Management of adverse drug reactions
4. Potential medication errors – Transfer of patients from capsule and tablet to liquid formulation and two dosing syringes.

**Rationale for the additional risk minimisation activity:**

Additional risk minimization activity is required to guide health care professionals on prescribing including patient selection, testing and monitoring for the above listed risks.

Also it is required for health care professionals, patients, parents/ caretakers for guidance on the management of such risks and how and where to report adverse reaction relevant to these risks.

**Target audience and planned distribution path:**

Health care professionals, patients and parents/carers.

Educational material will be distributed to health care professionals directly and patient/parents/carers will receive their educational material by the responsible health care professional.

**Plans to evaluate the effectiveness of the interventions and criteria for success:**

Effectiveness of educational materials will be measured via routine pharmacovigilance activities on annual basis as part of PSUR.

Please refer Annex 6: Details of Proposed Additional Risk Minimisation Measures.

## V.3 Summary of risk minimisation measures

A summary of pharmacovigilance activities and risk minimisation activities by safety concern is presented in Table 11 .

## Table 11 Summary of pharmacovigilance and risk minimisation activities

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| **Important Identified Risk** | | |
| **Identified Risk #1**<br>**Oligospermia and azoospermia with normal morphology and reduced semen volume** | Routine risk minimisation measures:<br>Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC: Section 4.6 (Fertility, pregnancy and lactation) and Section 4.8 (Undesirable effects).<br>Please refer to the Section 2 of the Xromi 100 mg/mL oral solution PL:<br>Pregnancy, breastfeeding and fertility.<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>Male patients should be informed by their healthcare professionals about the possibility of sperm conservation (cryopreservation) before the start of therapy. This recommendation has been added to Section 4.6 of the Xromi 100 mg oral solution SmPC and to Section 2 of the Xromi 100 mg/mL oral solution PL.<br><br>Additional risk minimisation measures:<br>A separate educational material for physician and patient/parent will be prepared to communicate this risk and provide further guidance. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>All the reports of impaired fertility will be monitored closely and will be presented in the PSUR.<br>Additional pharmacovigilance activities:<br>None. |
| **Important Potential Risks** | | |
| **Potential Risk #1**<br>**Potential medication errors – Transfer of patients from capsule and tablet to liquid formulation and two dosing syringes** | Routine risk minimisation measures:<br>Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC: Section 4.2 (Posology and Method of Administration).<br>Please refer to Section 3 of the Xromi 100 mg/mL oral solution PL where appropriate guidance is provided on taking the medicine along with instructional pictures:<br>How to take Xromi<br>Additional risk minimisation measures:<br>A separate educational material for physician and patient/parent will be prepared to communicate this risk and provide further guidance. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>All reports of medication errors will be monitored closely and will be reviewed in the PSUR.<br>Additional pharmacovigilance activities:<br>None. |
| **Potential Risk #2**<br>**The effect on embryogenesis, teratogenic potential, breastfeeding and post-natal development** | Routine risk minimisation measures:<br>Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC: Section 4.3 (Contraindications) and Section 4.6 (Fertility, pregnancy and lactation) and PL Section 2.<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:** | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific Follow-up Forms for Pregnancy and Breastfeeding<br>All reports of the effect on embryogenesis, teratogenic potential, breastfeeding and |

| | | |
|---|---|---|
| | The patient should be instructed to immediately contact a doctor in case of suspected pregnancy. Both male and female patients in reproductive age group should use effective methods of contraception before, during and after treatment with Xromi. The recommended duration of contraception in male and female patients following the end of treatment with Xromi should be 3 and 6 months, respectively. PL Section 2 instructions - Please contact your doctor immediately if you think you may be pregnant.<br>Additional risk minimisation measures:<br>A separate educational material for physician and patient/parent will be prepared to communicate this risk and provide further guidance. | post-natal development will be monitored closely and will be presented in the PSUR.<br>Additional pharmacovigilance activities:<br>None. |
| **Important Missing Information** | | |
| **Important Missing Information #1**<br>**Long-term safety in children below 2 years of age** | Routine risk minimisation measures:<br>Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC: Section 4.2 (Posology and method of administration) and Section 4.8 (Undesirable effects) and Section 2 of the PL.<br>Additional risk minimisation measures:<br>Not applicable. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>All reports of hydroxycarbamide use in patients below 2 years of age will be monitored closely and will be presented in the PSUR.<br>Additional pharmacovigilance activities:<br>A comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral solution 100 mg/ml) for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients under 2 years of age (PASS Study) will be conducted. |

Abbreviations: PK = pharmacokinetic; PL = Package leaflet; PSUR = Periodic safety update report; SmPC = Summary of Product Characteristics; PASS = post authorisation safety study.

# PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

Active substance(s): Hydroxycarbamide

Product(s) concerned: Xromi 100 mg/mL oral solution

MAH name: Lipomed GmbH.

Data lock point for this module: 03-Sep-2025

RMP version number when this module was last updated: 7.0

## 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 9 months 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 12.

**Table 12 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. Potential medication errors – Transfer of patients from capsule and tablet to liquid formulation and two dosing syringes<br>2. The effect on embryogenesis, teratogenic potential, breastfeeding and post-natal development |
| **Missing information** | 1. Long-term safety in children below 2 years of age |

## II.B Summary of important risks

A summary of important identified/potential risks/missing information is provided in Table 13.

**Table 13 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:<br>Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC:<br>Section 4.6 (Fertility, pregnancy and lactation) and Section 4.8 (Undesirable effects).<br>Please refer to the Section 2 of the Xromi 100 mg/mL oral solution PL:<br>Pregnancy, breastfeeding and fertility.<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>Male patients should be informed by their healthcare professionals about the possibility of sperm conservation (cryopreservation) before the start of therapy. This recommendation has been added to Section 4.6 of the Xromi 100 mg oral solution SmPC and to Section 2 of the Xromi 100 mg/mL oral solution PL.<br>Additional risk minimisation measures:<br>Additional risk minimization will be undertaken by communicating this risk to physicians/healthcare providers and patients, using educational materials. |
| **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 the previous MAH 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:<br>Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC: Section 4.2 (Posology and Method of Administration).<br>Please refer to Section 3 of the Xromi 100 mg/mL oral solution PL where appropriate guidance is provided on taking the medicine along with instructional pictures:<br>How to take Xromi<br>Additional risk minimisation measures:<br>Additional risk minimization will be undertaken by communicating this risk to physicians/healthcare providers and patients, using educational materials. |
| **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:<br>Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC: Section 4.3 (Contraindications) and Section 4.6 (Fertility, pregnancy and lactation) and PL Section 2.<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>The patient should be instructed to immediately contact a doctor in case of suspected pregnancy. Both male and female patients in reproductive age group should use effective methods of contraception before, during and after treatment with Xromi. The recommended duration of contraception in male and female patients following the end of treatment with Xromi should be 3 and 6 months, respectively. PL Section 2 instructions - Please contact your doctor immediately if you think you may be pregnant.<br>Additional risk minimisation measures:<br>Additional risk minimization will be undertaken by communicating this risk to physicians/healthcare providers and patients, using educational materials. |
| **Missing information: Long-term safety in children below 2 years of age** | |
| **Risk minimisation measures** | Routine risk minimisation measures:<br>Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC: Section 4.2 (Posology and method of administration) and Section 4.8 (Undesirable effects) and Section 2 of the PL.<br>Additional risk minimisation measures:<br>None. |
| **Additional pharmacovigilance activities** | A comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral solution 100 mg/ml) for the prevention of vaso-occlusive complications of Sickle Cell Disease in children under 2 years of age (PASS Study) will be conducted. |

Abbreviations: 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

**Study short name:**

PASS of Xromi comparing safety and effectiveness in children under 2 years with Sickle cell disease.

Comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral solution 100 mg/ml) for the prevention of vaso-occlusive complications of Sickle Cell Disease in children under 2 years of age.

Purpose of the study:

As part of the extension of indication to include the prevention of vaso-occlusive complications of sickle cell disease in children from 9 months to 2 years of age for Xromi (variation II/0019), the authorities requested additional safety and efficacy data to further establish the risk benefit profile of hydroxycarbamide in infants between the age of 9 months and 2 years. This study is aiming to collect further data on the long term safety of Xromi in children below 2 years of age.

The main study objectives are summarised below:

- Primary Objective: Assessment of the incidence of adverse events of special interest (AESIs) in children who have SCD and are treated with hydroxycarbamide oral solution 100 mg/ml (Xromi), in comparison to a retrospective comparator cohort.

Secondary objective:

- Assessment of the effectiveness of Xromi for the clinical events and laboratory tests and physiological assessments of interest, in comparison to a retrospective comparator cohort.

Exploratory Objectives:

- To assess the overall safety of Xromi by describing AEs by severity, seriousness, relatedness, action taken, outcome, and duration.
- To describe occurrence of and reasons for discontinuation of Xromi.
- To assess the safety of Xromi at the optimised dose.
- To assess if the effectiveness of Xromi is associated with the dose.

- To assess the safety and effectiveness of Xromi by subgroups (age, sex, SCD subtypes, country).
- To assess occurrence of clinical events in comparators exposed to any formulation of hydroxycarbamide during follow-up.
- To assess organ function and potential preservation in children exposed to any formulation of hydroxycarbamide.

**ANNEXES**

## Annex 4: Specific Adverse Event Follow-Up Forms

**Pregnancy**

**Pregnancy Report Form**

**Send to LIPOMED PV AND SAFETY E-MAIL:**
save@lipomed.com

*Part 1: This form is to be used as an INITIAL notification that a pregnancy has occurred.*

Date Reporter notified of Pregnancy: _____ -_____ -_____ (DD MMM YYYY)

Date of this Report: _____ -_____ -_____ (DD MMM YYYY)

**Patient Information**

Year of Birth: _____ (YYYY)

☐ Female (Maternal Exposure) ☐ Male (Paternal Exposure)

**Pregnancy Information**

Method of Birth Control (if applicable):_____

Pregnancy Initially Diagnosed by (check all that apply): ☐ Home Urine test ☐ Outpatient department Urine test ☐ Serum test

Start date of last period: _____ -_____ -_____ (DD MMM YYYY) Date Pregnancy Confirmed: _____ -_____ -_____ (DD MMM YYYY)

Anticipated due date: _____ -_____ -_____ (DD MMM YYYY) Methodology for calculation: ultrasound ☐ Manual calculation method ☐ Other (specify).....

| Prenatal tests completed: | | |
|---|---|---|
| | ☐ (MS) AFP __ -___ -_____ DD-MM-YYYY | ☐ Amniocentesis __ -___ -_____ DD-MM-YYYY |
| | ☐ Ultrasound __ -___ -_____ DD-MM-YYYY | ☐ Other (specify) __ -___ -_____ DD-MM-YYYY |

Was there evidence of a birth defect or genetic disorder from prenatal test? ☐ No ☐ Yes

| If Yes, indicate which tests(s) revealed evidence of birth defects. (Add details to additional information section) | ☐ (MS) AFP ☐ Amniocentesis _ |
|---|---|
| | ☐ Ultrasound ☐ Other (specify) _ |

**Medical History**

**Obstetric History:**
Number of Pregnancies: _____ Number of Births:_____ Number of Miscarriages:_____
Number of Terminations:_____

**Medical History Relevant to Pregnancy (including conception and fertility history(e.g. subfertility), pregnancy risk factors, previous maternal pregnancy complications, previous foetal/neonatal abnormalities, smoking, alcohol, environmental or chemical hazards, etc.):**

**Drugs Taken During Pregnancy**

| Product(s) | Total Daily Dose (mg) | Duration of Therapy (DD-MMM-YYYY) | | Indication |
|---|---|---|---|---|
| | | Started | Stopped | |
| | | | | |
| | | | | |

Pregnancy Report Form_v01_20250526 Page 1 of 2

**Pregnancy**

| Pregnancy Report Form | | | | | |
|---|---|---|---|---|---|
| Send to LIPOMED PV AND SAFETY E-MAIL: save@lipomed.com | | | | | |
| *Part 1: This form is to be used as an INITIAL notification that a pregnancy has occurred.* | | | | | |
| | | | | | |
| | | | | | |
| **Additional Information** | | | | | |
| **Attending Obstetrician** | **Name & Address / Contact Details:**<br>**Name:** _____<br>**Address:** _____<br>_____<br>**Telephone Number:** _____ **Fax Number:** _____ | | | | |
| **Reporter** | **Pregnancy Reported By:**<br>**Print Name:** _____<br>**Signature:** _____ **Date:** _____-_____-_____ (DD MMM \YYYY) | | | | |

**IMPORTANT**: Please **do not** send additional documents with this Pregnancy form, but add any relevant information to the Pregnancy form itself.

**NOTE**: Please ensure **Personal Information** that could **potentially identify the patient is not included in any document** that is sent to **LIPOMED** as per **ICH GCP Principles 2.11, EU General Data Protection Regulation (GDPR)** and other **applicable laws and legislations.**

**Pregnancy Follow-up**

**Pregnancy Follow-up form**

**Send to LIPOMED PV AND SAFETY E-MAIL:**
save@lipomed.com

*Part II: This form is to be used as a FOLLOW-UP notification regarding the outcome of the pregnancy.*

**Patient Information**

Date of Report: _____-_____-_____ (DD MMM YYYY) Year of Birth _____ (YYYY)

☐ Female (Maternal Exposure) ☐ Male (Paternal Exposure) ☐ No further information available (Please provide details):

**Course of Pregnancy**

**List any exposure(s) during the course of the pregnancy:**

Smoking: _____ cig./day Alcohol: _____ glasses/day

Substance Abuse: ☐ No ☐ Yes, Specify: _____

Environmental or Chemical Hazards: ☐ No ☐ Yes, Specify:

Any previous family history of congenital abnormality, psychomotor retardation ( specify paternal/maternal and relationship):

Consanguinity between parents ( specify degree):

**List any significant illness(es) during the course of the pregnancy:**

**Pregnancy Outcome**

Date of Delivery: _____-_____-_____ (DD MM YYYY) Live Newborn: ☐ Yes ☐ No | Details: _____

Mode of Delivery: ☐ Vaginal ☐ Assisted Vaginal ☐ Caesarian

Malformations/anomalies diagnosed in foetus or at birth: ☐ Yes ☐ No

Dysmaturity: ☐ Yes ☐ No

Placenta Normal: ☐ Yes ☐ No

Gestational age at birth:.....

Delivery complications (foetal distress, amniotic fluid abnormal, etc) :

.....

.....

**Condition of Newborn**

Gender: ☐ Female ☐ Male Weight: _____ kg _____ Lbs Length: _____ cm _____ inches

Head Circumference _____ cm _____ inches

APGAR Score: 1 minute: _____ 5 minutes: _____

Additional details ( if twin pregnancy, multiple pregnancy, etc.) :

.....

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**Pregnancy Follow-up**

**Pregnancy Follow-up form**

**Send to LIPOMED PV AND SAFETY E-MAIL:**
save@lipomed.com

***Part II: This form is to be used as a FOLLOW-UP notification regarding the outcome of the pregnancy.***

**Follow up for neonatal information:**

Date of information: .....

Source of information: .....

Malformation/anomalies diagnosed and (cyto)genetic testing results obtained since initial report.....

Developmental assessment.....

**Termination/Abortion Information**

Reason for Termination: _____

Results of Physical Examination (Gender, external anomalies) and Pathology _____

_____

_____

Gestation Age at Termination: _____(days/weeks)

**Concomitant Drugs/Treatment Taken During Pregnancy**

| Drug Name/Treatment | Total Daily Dose (mg) | Duration of Therapy (DD-MMM-YYYY) | | Indication |
|---|---|---|---|---|
| | | Started | Stopped | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

**Additional Information**

**(Such as, relevant medical history (including paternal history), Neonatal illness, hospitalization, drug therapies)**

**Attending Obstetrician**

**Name & Address / Contact Details:**

**Name:** _____

**Address:** _____

_____

**Telephone Number:** _____ **Fax Number:** _____

**Pregnancy Follow-up**

| Pregnancy Follow-up form | |
|---|---|
| Send to LIPOMED PV AND SAFETY E-MAIL: save@lipomed.com | |
| *Part II: This form is to be used as a FOLLOW-UP notification regarding the outcome of the pregnancy.* | |
| Reporter | **Pregnancy Reported By:**<br>**Print Name:** _____<br>**Signature:** _____ **Date:** _____-_____-_____ (DD MMM YYYY) |

**IMPORTANT**: Please **do not** send additional documents with this pregnancy follow-up form, but add any relevant information to the pregnancy follow-up form itself.

**NOTE**: Please ensure **Personal Information** that could **potentially identify the patient is not included in any document** that is sent to **LIPOMED** as per **ICH GCP Principles 2.11, EU General Data Protection Regulation (GDPR)** and other **applicable laws and legislations.**

**BREAST FEEDING REPORT FORM *(IN CONFIDENCE)***

*PLEASE COMPLETE THIS FORM AND RETURN TO*
E-MAIL: **save@lipomed.com** *AFTER DELIVERY OF THE BABY*

REPORTER'S DETAILS:

NAME: _____

POSITION: _____

ADDRESS: _____

_____

COUNTRY: _____

PHARMACOVIGILANCE USE ONLY

AE No. _____

Receipt Date: ____/____/____ (DD/MM/YY)

TELEPHONE: _____

**Maternal data:**

| Mother's initials. | Age / D.O.B. (YYYY) | Weight |
|---|---|---|
| | | |

**Infant data:**

| Infant's initials | D.O.B. | Gestational age at birth | Sex of baby | Birth Weight (kg) | Date of breastfeeding | |
|---|---|---|---|---|---|---|
| | | | | | Start | Stop |
| | | | | | | |

**DRUG EXPOSURE DURING BREAST FEEDING** (please list all drugs taken during this time):

| Drug Name | Daily dose | Route | Start date | Stop date |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

Has the infant suffered any development problems or adverse events whilst breast feeding? ☐ Yes ☐ No
If yes, please complete the attached AE/SAE FORM.

Has the mother experienced adverse events associated with the drugs taken whilst breast feeding? ☐ Yes ☐ No
If yes, please complete the attached AE/SAE FORM.

REPORTER'S SIGNATURE: _____ Date: ____/____/____
DD/MM/YY

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Pregnancy Follow-up

## Nova Laboratories Pregnancy Follow-up form

**Send to ICON PV AND SAFETY SERVICES E-MAIL:**
**ICON-Safety-CentralReceipt@iconplc.com (ROW)**

*Part II: This form is to be used as a FOLLOW-UP notification regarding the outcome of the pregnancy.*

**Patient Information**

Date of Report: - - Year of Birth
DD MMM YYYY YYYY

☐ Female (Maternal Exposure) ☐ Male (Paternal Exposure) ☐ No further information available (Please provide details):

**Course of Pregnancy**

**List any exposure(s) during the course of the pregnancy:**

Smoking: _____ cig./day Alcohol: _____ glasses/day

Substance Abuse: ☐ No ☐ Yes, Specify: _____

Environmental or Chemical Hazards: ☐ No ☐ Yes, Specify:

Any previous family history of congenital abnormality, psychomotor retardation ( specify paternal/maternal and relationship):

Consanguinity between parents ( specify degree):

**List any significant illness(es) during the course of the pregnancy:**

**Pregnancy Outcome**

Date of Delivery: _____ DD MM YYYY Live Newborn: ☐ Yes ☐ No Details: _____

Mode of Delivery: ☐ Vaginal ☐ Assisted Vaginal ☐ Caesarian

Malformations/anomalies diagnosed in foetus or at birth: ☐ Yes ☐ No

Gestational age at birth:.....

Dysmaturity: ☐ Yes ☐ No

Placenta Normal: ☐ Yes ☐ No

Delivery complications (foetal distress, amniotic fluid abnormal, etc) :
.....
.....

**Condition of Newborn**

Gender: ☐ Female ☐ Male Weight: _____ kg _____ Lbs Length: _____ cm _____ inches

Head Circumference _____ cm inches

APGAR Score: 1 minute: _____ 5 minutes: _____

Additional details ( if twin pregnancy, multiple pregnancy, etc.) :
.....

Pregnancy Follow-up v04 Effective 30Sep2022 Page 1 of 3

## Annex 6: Details of proposed additional risk minimisation activities

Prior to the launch of Xromi 100 mg/mL oral solution in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at the preparation of a separate educational material for physician and patient/parent/carers to communicate the important identified risks and important potential risks to the physician/healthcare professionals, patient/parent/carer as a part of additional risk minimisation activities.

The MAH shall ensure that in each Member State where Xromi 100 mg/ mL oral solution is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Xromi 100 mg/ mL oral solution have access to/are provided with the following educational package:

- **Physician and Patient/ Parent guide**

Key messages of additional risk minimization activities:

**Physician guide:**

- Indication, dosage and dose adjustment: Information on Xromi, including the approved indication, daily dose and dose adjustment according to the SmPC.
- Handling of Xromi: description of safe handling of Xromi according to SmPC.
- Warnings about important risks associated with using Hydroxycarbamide:
  - Switching patients from capsule and tablet to liquid formulation and two dosing syringes- With conversion there is titration possibility of an impact on dose although Xromi 100 mg/mL oral solution is considered bioequivalent and therefore interchangeable as per the data available from the bioequivalence study. Consideration should be given to a potential risk of medication error with the use of two syringes (3 mL and 10 mL) for dose calculation and administration.
  - Need for contraception.
  - Risk to male and female fertility, potential risk to foetus and breast feeding.
  - Management of adverse drug reactions.
- Summary of Product Characteristics – refer to Xromi SmPC.

**Patient/ Parent guide:**

- Proper and safe use of the product:
  - Each pack contains one bottle 150 ml capped with a child-resistant closure, a bottle adaptor and two dosing syringes (a syringe graduated to 3 ml and a syringe graduated to 10 ml).
  - 3 ml syringe- to be used if total dose is less than or equal to 3 ml, each graduation of 0.1 ml contains 10 mg of hydroxycarbamide.
  - 10 ml syringe- to be used if the total amount you have is more than 3 ml, each graduation of 0.5 ml contains 50 mg of hydroxycarbamide.
  - Please use the syringe as advised by your doctor or pharmacist to avoid the risk of medication error.
  - Women who are pregnant, planning to be or breast feeding should not handle Xromi.
  - Xromi may be taken with or after meals at any point of the day.
  - Water should be taken after each dose of Xromi to assist accurate and consistent dose of delivery to stomach.
  - For proper handling of the product please refer to the package leaflet.
- Need for contraception.

  Risk to male and female fertility, potential risk to foetus and breast feeding.
- Package Leaflet– refer to Xromi Package Leaflet.