ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xromi 100 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 100 mg hydroxycarbamide.

Excipients with known effect
One ml of solution contains 0.5 mg methyl hydroxybenzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.
Clear, colourless to pale yellow viscous liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xromi is indicated for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 9 months of age.

4.2 Posology and method of administration

Hydroxycarbamide treatment should be supervised by a physician or other healthcare professionals experienced in the management of patients with Sickle Cell Disease.

Posology
The posology should be based on the patient's body weight (kg).
The usual starting dose of hydroxycarbamide is 15 mg/kg/day and the 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.

A target absolute neutrophil count 1,500 – 4,000/ μL should be aimed for, whilst maintaining platelet count > 80,000/ μL. If neutropenia or thrombocytopenia occurs, hydroxycarbamide dosing should be temporarily withheld and full blood cell count with white cell differential should be monitored weekly. When blood counts have recovered, hydroxycarbamide should be reinstated at a dose 5 mg/kg/day lower than the dose given before onset of cytopenias.

If dose escalation is warranted based on clinical and laboratory findings, the following steps should be taken:
- Dose to be increased by 5 mg/kg/day increments every 8 weeks.
- Increases in dose to be continued until mild myelosuppression (absolute neutrophil count 1,500/ μL to 4,000/ μL) is achieved, up to a maximum of 35 mg/kg/day.
- Full blood cell count with white cell differential and reticulocyte count to be monitored at least every 4 weeks when adjusting dosage.

Once a maximum tolerated dose is established, laboratory safety monitoring should include full blood cell count with white cell differential, reticulocyte count, and platelet count every 2-3 months.

Red blood cell (RBC), mean cell volume (MCV), and foetal haemoglobin (HbF) levels should be monitored for evidence of consistent or progressive laboratory response. However, a lack of increase in MCV, HbF, or both, is not an indication to discontinue therapy if the patient responds clinically (e.g. decreased incidence of pain or hospitalisation).

A clinical response to treatment with hydroxycarbamide may take 3-6 months and therefore, a 6- month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure (whether due to lack of adherence or failure to respond to therapy).

Special populations

Elderly
Elderly patients may be more sensitive to the myelosuppressive effects of hydroxycarbamide, and may require a lower dosage regimen.

Renal impairment
Since renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of hydroxycarbamide in renally impaired patients. In patients with a creatinine clearance (CrCl) ≤ 60 ml/min the initial hydroxycarbamide dose should be decreased by 50%. Close monitoring of blood parameters is advised in these patients (see section 4.4).
Hydroxycarbamide must not be administered to patients with severe renal impairment (CrCl < 30 ml/min) (see sections 4.3, 4.4, and 5.2).

Hepatic impairment
There are no data that support specific dose adjustments in patients with hepatic impairment. Close monitoring of blood parameters is advised in these patients. Due to safety considerations, hydroxycarbamide is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 4.4).

Children less than 9 months of age
The safety and efficacy of hydroxycarbamide in children from birth up to 9 months of age have not yet been established.

Method of administration
Xromi is for oral use.

Two dosing syringes (a 3 ml and a 10 ml) are provided for accurate measurement of the prescribed dose of the oral solution. It is recommended that the healthcare professional advises the patient or carer which syringe to use to ensure that the correct volume is administered.

The smaller 3 ml syringe, marked from 0.5 ml to 3 ml, is for measuring doses of less than or equal to 3 ml. This syringe should be recommended for doses less than or equal to 3 ml (each graduation of 0.1 ml contains 10 mg of hydroxycarbamide).
The larger 10 ml syringe, marked from 1 ml to 10 ml, is for measuring doses of more than 3 ml. This syringe should be recommended for doses greater than 3 ml (each graduation of 0.5 ml contains 50 mg of hydroxycarbamide).

In adults without swallowing difficulties, solid oral formulations may be more appropriate and convenient.

Xromi may be taken with or after meals at any time of the day but patients should standardise the method of administration and time of day.

To assist accurate and consistent dose delivery to the stomach water should be taken after each dose of Xromi.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Severe hepatic impairment (Child-Pugh classification C).
Severe renal impairment (CrCl < 30 ml/min).
Toxic ranges of myelosuppression as described in section 4.2.
Breast-feeding (see section 4.6).
Pregnancy (see section 4.6)
Concomitant anti-retroviral medicinal products for HIV disease (see sections 4.4 and 4.5)

4.4 Special warnings and precautions for use

Bone marrow suppression
The complete status of the blood, including bone marrow examination, if indicated, as well as kidney function and liver function should be determined prior to, and repeatedly during, treatment. If bone marrow function is depressed, treatment with hydroxycarbamide should not be initiated.
The full blood cell count with white cell differential, reticulate count, and platelet count should be monitored regularly (see section 4.2).
Hydroxycarbamide may produce bone marrow suppression; leukopenia is generally its first and most common manifestation. Thrombocytopenia and anaemia occur less often and are seldom seen without a preceding leukopenia. Bone marrow depression is more likely in patients who have previously received radiotherapy or cytotoxic cancer chemotherapeutic medicinal products; hydroxycarbamide should be used cautiously in such patients. The recovery from myelosuppression is rapid when hydroxycarbamide therapy is interrupted.
Hydroxycarbamide therapy can then be re-initiated at a lower dose (see section 4.2).

Severe anaemia must be corrected with whole blood replacement before initiating therapy with hydroxycarbamide. If, during treatment, anaemia occurs, correct without interrupting hydroxycarbamide therapy. Erythrocytic abnormalities; megaloblastic erythropoiesis, which is self- limiting, is often seen early in the course of hydroxycarbamide therapy. The morphologic change resembles pernicious anaemia, but is not related to vitamin B_{12} or folic acid deficiency. The macrocytosis may mask the incidental development of folic acid deficiency; regular determinations of serum folic acid are recommended. Hydroxycarbamide may also delay plasma iron clearance and reduce the rate of iron utilisation by erythrocytes but it does not appear to alter the red blood cell survival time.

Other
Patients who have received irradiation therapy in the past may have an exacerbation of post irradiation erythema when hydroxycarbamide is given.

Renal and hepatic impairment
Hydroxycarbamide should be used with caution in patients with marked renal dysfunction.
Hydroxycarbamide may cause hepatotoxicity and liver function tests should be monitored during treatment.
Blood parameters for renal and hepatic impairment should be closely monitored, and hydroxycarbamide should be discontinued if necessary. If appropriate, hydroxycarbamide should be re-started at a lower dose.

HIV patients
Hydroxycarbamide must not be used in combination with anti-retroviral medicinal products for HIV disease and it may cause treatment failure and toxicities (in some cases fatal) in HIV patients (see sections 4.3 and 4.5).

Secondary leukaemia and skin cancer
In patients receiving long-term therapy with hydroxycarbamide for myeloproliferative disorders, such as polycythaemia, secondary leukaemia has been reported. It is unknown whether this leukaemogenic effect is secondary to hydroxycarbamide or associated with the patient's underlying disease. Skin cancer has been reported in patients receiving long-term hydroxycarbamide. Patients should be advised to protect skin from sun exposure. In addition patients should conduct self - inspection of the skin during the treatment and after discontinuation of the therapy with hydroxycarbamide and be screened for secondary malignancies during routine follow-up visits.

Cutaneous vasculitic toxicities
Cutaneous vasculitic toxicities including vasculitic ulcerations and gangrene have occurred in patients with myeloproliferative disorders during therapy with hydroxycarbamide. The risk of vasculitic toxicities is increased in patients who receive prior or concomitant interferon therapy. The digital distribution of these vasculitic ulcerations and progressive clinical behaviour of peripheral vasculitic insufficiency leading to digital infarct or gangrene were distinctly different than the typical skin ulcers generally described with Hydroxycarbamide. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease, hydroxycarbamide should be discontinued if cutaneous vasculitic ulcerations develop.

Vaccinations
Concomitant use of hydroxycarbamide with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase some of the adverse reactions of the vaccine virus because normal defence mechanisms may be suppressed by hydroxycarbamide. Vaccination with a live vaccine in a patient taking hydroxycarbamide may result in severe infection. The patient's antibody response to vaccines may be decreased. The use of live vaccines should be avoided during treatment and for at least six months after treatment has finished and individual specialist advice sought (see section 4.5).

Leg ulcers
In patients with leg ulcers, hydroxycarbamide should be used with caution. Leg ulcers are a common complication of Sickle Cell Disease, but have also been reported in patients treated with hydroxycarbamide.

Carcinogenicity
Hydroxycarbamide is unequivocally genotoxic in a wide range of test systems. Hydroxycarbamide is presumed to be a transspecies carcinogen (see section 5.3).

Limbal stem cell deficiency
Cases of limbal stem cell deficiency have been reported during treatment with hydroxycarbamide. In some cases, limbal stem cell deficiency improved after treatment discontinuation. Patients presenting with relevant signs and symptoms (reduced/impaired vision, photophobia, redness, and pain) should be referred to an ophthalmologist. If limbal stem cell deficiency is confirmed, discontinuation of the treatment should be considered.

Safe handling of the solution
Parents and care givers should avoid hydroxycarbamide contact with skin or mucous membrane. If the solution comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water (see section 6.6).

Excipients
This medicinal product contains methyl parahydroxybenzoate (E218) which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

The myelosuppressive activity may be potentiated by previous or concomitant radiotherapy or cytotoxic therapy.

Concurrent use of hydroxycarbamide and other myelosuppressive medicinal products or radiation therapy may increase bone marrow depression, gastro-intestinal disturbances or mucositis. An erythema caused by radiation therapy may be aggravated by hydroxycarbamide.
Patients must not be treated with hydroxycarbamide and anti-retroviral medicinal products concurrently (see sections 4.3 and 4.4).
Fatal and non-fatal pancreatitis has occurred in HIV-infected patients during therapy with hydroxycarbamide and didanosine, with or without stavudine.
Hepatotoxicity and hepatic failure resulting in death were reported during post-marketing surveillance in HIV-infected patients treated with hydroxycarbamide and other antiretroviral medicinal products. Fatal hepatic events were reported most often in patients treated with the combination of hydroxycarbamide, didanosine, and stavudine.
Peripheral neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving hydroxycarbamide in combination with anti-retroviral medicinal products, including didanosine, with or without stavudine (see section 4.4).

Patients treated with hydroxycarbamide in combination with didanosine, stavudine, and indinavir showed a median decline in CD4 cells of approximately 100/ mm^3.

Studies have shown that there is an analytical interference of hydroxycarbamide with the enzymes (urease, uricase, and lactic dehydrogenase) used in the determination of urea, uric acid, and lactic acid, rendering falsely elevated results of these in patients treated with hydroxycarbamide.

Vaccinations
There is an increased risk of severe or fatal infections with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients.
Concomitant use of hydroxycarbamide with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase the adverse reaction of the vaccine virus, because normal defence mechanisms may be suppressed by hydroxycarbamide therapy. Vaccination with a live vaccine in a patient taking hydroxycarbamide may result in severe infections. Generally, the patient's antibody response to vaccines may be decreased. Treatment with hydroxycarbamide and concomitant immunisation with live virus vaccines should only be performed if benefits clearly outweigh potential risks (see section 4.4).

Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders during therapy with hydroxycarbamide. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy (see section 4.4).

Interference with Continuous Glucose Monitoring systems
Hydroxycarbamide may falsely elevate sensor glucose results from certain continuous glucose monitoring (CGM) systems and may lead to hypoglycaemia if sensor glucose results are relied upon to dose insulin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Medicinal products which affect DNA synthesis, such as hydroxycarbamide, may be potent mutagenic active substances. This possibility should be carefully considered before administering this medicinal product to male or female patients who may contemplate conception.
Both male and female patients should be advised to use contraceptive measures before, during and after treatment with hydroxycarbamide. The recommended duration of contraception in male and female patients following the end of treatment with hydroxycarbamide, should be 3 and 6 months, respectively.

Pregnancy
Studies in animals have shown reproductive toxicity (see section 5.3). Patients on hydroxycarbamide should be made aware of the risks to the foetus.

There is limited amount of data from the use of hydroxycarbamide in pregnant women.

Hydroxycarbamide can cause foetal harm when administered to a pregnant woman. Therefore it must not be administered to patients who are pregnant.

Patients on hydroxycarbamide wishing to conceive should stop treatment 3 to 6 months before pregnancy if possible.
The patient should be instructed to immediately contact a doctor in case of suspected pregnancy.

Breast-feeding
Hydroxycarbamide is excreted in human breast milk. Because of the potential for serious adverse reactions in breast-feeding infants, breast-feeding must be discontinued while taking hydroxycarbamide.

Fertility
Fertility in males might be affected by treatment. Very common reversible oligo- and azoospermia have been observed in man, although these disorders are also associated with the underlying disease. Impaired fertility has been observed in male rats (see section 5.3).
Male patients should be informed by their healthcare professionals about the possibility of sperm conservation (cryopreservation) before the start of therapy.

4.7 Effects on ability to drive and use machines

Hydroxycarbamide has minor influence on the ability to drive and use machines. Patients should be advised not to drive or operate machines, if dizziness is experienced while taking hydroxycarbamide.

4.8 Undesirable effects

The safety profile of hydroxycarbamide in sickle cell disease was established from clinical studies and confirmed with long-term cohort studies including up to 1935 adults and children of more than 9 months of age.

Summary of the safety profile
Bone-marrow suppression is the major toxic effect of hydroxycarbamide and is dose related. At lower doses, mild, transient and reversible cytopenias are commonly reported in Sickle Cell Disease patients which is expected based on the pharmacology of hydroxycarbamide.
Hydroxycarbamide affects spermatogenesis, and hence oligospermia and azoospermia are very commonly reported.
Other commonly reported adverse effects also include nausea, constipation, headache, and dizziness.
Adverse reactions affecting the skin and subcutaneous tissue such as darkening of the skin nail beds, dry skin, skin ulcers, and alopecia tend to occur following several years of long-term daily maintenance therapy. Rarely leg ulcers and very rarely systemic lupus erythematosus have been reported.
There is also a serious risk of leukaemia and in the elderly, skin cancer, although the frequency is not known.

Tabulated list of adverse reactions
The list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), and not known (cannot be estimated from the available data).

Table 1: Adverse reactions

System organ class	Frequency	Adverse reaction
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Not known	Leukaemia, skin cancers (in elderly patients)
Blood and lymphatic system disorders	Very common	Bone marrow depression including neutropenia (< 1,500 / μL), reticulocytopenia (< 80,000 / μL), macrocytosis
	Common	Thrombocytopenia (< 80,000 / μL), anaemia (haemoglobin < 4.5 g/dl)
Metabolism and nutrition disorders	Not known	Weight gain, vitamin D deficiency
Nervous system disorders	Common	Headache, dizziness
Eye disorders	Not known	Limbal stem cell deficiency
Vascular disorders	Not known	Bleeding
Gastrointestinal disorders	Common	Nausea, constipation
	Uncommon	Stomatitis, diarrhoea, vomiting
	Not known	Gastrointestinal disturbances, gastrointestinal ulcer, severe hypomagnesaemia
Hepatobiliary disorders	Uncommon	Elevated liver enzymes, Hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Skin ulcer, oral, nail and skin hyperpigmentation, dry skin, alopecia
	Uncommon	Rash
	Rare	Leg ulcers
	Very Rare	Systemic and cutaneous lupus erythematosus
Reproductive system and breast disorders	Very common	Oligospermia, azoospermia
	Not known	Amenorrhea
General disorders and administration site conditions	Not known	Fever

Description of selected adverse reactions

In the event of bone marrow suppression, haematological recovery usually occurs within two weeks of withdrawal of hydroxycarbamide. Gradual dose titration is recommended to avoid more severe bone marrow suppressions (see section 4.2).

The macrocytosis caused by hydroxycarbamide is not vitamin B_{12} or folic acid dependent. The anaemia commonly observed has mainly been due to an infection with Parvovirus, splenic or hepatic sequestration, renal impairment.

Weight gain observed during treatment with hydroxycarbamide may be an effect of improved general conditions.
Oligospermia and azoospermia caused by hydroxycarbamide are in general reversible, but have to be taken into account when fatherhood is desired (see section 5.3). These disorders are also associated with the underlying disease.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be similar to adults. Data from an observational study (ESCORT-HU) of hydroxycarbamide in a large set of patients (n=1 906) with sickle cell disease showed that patients aged 2 to 10 years were at higher risk for neutropenia and at lower risk for dry skin, alopecia, headache and anaemia. Patients aged 10 to 18 years were at lower risk for dry skin, skin ulcer, alopecia, weight increase and anaemia compared to adults.

Safety data in children under the age of 2 years is limited. The BABY HUG trial, a phase III double-blinded, multi-centre, randomised, controlled study in infants aged 9 – 18 months, compared fixed moderate dose hydroxycarbamide at 20 mg/kg/day with placebo (Wang et al. 2011). Mild-to-moderate neutropenia (absolute neutrophil count [ANC] 500–1249/ µL), occurred more frequently in the hydroxycarbamide group; 107 times in 45 participants versus 34 times in 18 participants in the placebo group. Recurrent or persistent neutropenia resulted in nine long-term dose decreases (to 17·5 mg/kg per day) in the hydroxycarbamide group and five in the placebo group (p=0·20). Infants treated with hydroxycarbamide did not have significant differences from those treated with placebo in rates of severe neutropenia (ANC <500/ µL), thrombocytopenia (platelet count <80,000/ µL), anaemia (haemoglobin <7 g/dL), reticulocytopenia (absolute reticulocyte count <80,000/ µL), or abnormal tests of liver function (alanine aminotransferase >150 units/L or bilirubin >10 mg/dL).

The safety of Xromi has been assessed in 32 children aged 9 months - 18 years with sickle cell anaemia in a single-arm, open-label, prospective, multi-center, pharmacokinetic, safety and efficacy study (HUPK study). The total number of hydroxycarbamide-related adverse events was 28 (8.3%) in 9 (28%) patients. Haematological toxicity dominated with 21 reports (75%) of cytopenias and then skin and subcutaneous disorders (5 reports; 18%). The 9 months to 2 year age group had 19 related events (29.2%), a higher proportion compared to the 2 to 6 year group (5 events; 3.4%) and 6 to 16 year group (4 events; 3.2%). The reported cytopenias were typically isolated, transient and benign.

The long term safety of hydroxycarbamide initiated in children less than 2 years remains to be established.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Acute mucocutaneous toxicity has been reported in patients receiving hydroxycarbamide at a dosage several times greater than that recommended. Soreness, violet erythema, oedema on palms and foot soles followed by scaling of hands and feet, intense generalised hyperpigmentation of skin, and severe acute stomatitis were observed.
In patients with sickle cell disease, severe bone marrow depression was reported in isolated cases of hydroxycarbamide overdose between 2 and 10 times the prescribed dose (up to 8.57 times of the maximum recommended dose of 35 mg/kg/day). It is recommended that blood counts are monitored for several weeks after overdose since recovery may be delayed.

Treatment
Immediate treatment consists of gastric lavage, followed by supportive therapy for the cardiorespiratory systems if required. Patients should be monitored for vital signs, blood and urine chemistry, renal and hepatic function and full blood counts for at least 3 weeks. Longer periods of monitoring may be required. If necessary, blood should be transfused.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX05.

Mechanism of action
Hydroxycarbamide is an orally active antineoplastic agent.
Although the mechanism of action has not yet been clearly defined, hydroxycarbamide appears to act by interfering with synthesis of DNA by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or protein.

One of the mechanisms by which hydroxycarbamide acts is the elevation of HbF concentrations in Sickle Cell Disease patients. HbF interferes with the polymerisation of HbS (sickle haemoglobin) and thus impedes the sickling of red blood cell. In all clinical studies, there was a significant increase in HbF from baseline after hydroxycarbamide use.
Recently, hydroxycarbamide has shown to be associated with the generation of nitric oxide suggesting that nitric oxide stimulates cyclic guanosine monophosphatase (cGMP) 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, improved deformability of sickled cells, and altered adhesion of red blood cells to the endothelium.

Clinical efficacy and safety
Evidence for the efficacy of hydroxycarbamide in reducing the vaso-occlusive complications of Sickle Cell Disease in children older than 9 months comes from five randomised controlled studies (Charache *et al* 1995 [MSH Study]; Jain *et al* 2012, Ferster *et al* 1996; Ware *et al* 2015 [TWiTCH], Wang *et al* 2011 [BABY HUG]). Furthermore, findings from these pivotal studies are supported by observational studies including some long-term follow up.

Multi-centre study of hydroxycarbamide in Sickle Cell Anaemia (MSH)
The MSH study was a multicentre, randomised, and double-blind study, which compared hydroxycarbamide with placebo in adults with Sickle Cell Anaemia (HbSS genotype only) with the objective of reducing the frequency of pain crises. A total of 299 participants were randomised; 152 to hydroxycarbamide and 147 to matching placebo. Hydroxycarbamide was started at low dose (15 mg/kg per day) and increased at 12-weekly intervals by 5 mg/kg per day until mild bone marrow depression was achieved, as judged by either neutropenia or thrombocytopenia. Once the blood count had recovered, treatment was restarted at 2.5 mg/kg per day less than the toxic dose.
There was a statistically significant difference between the hydroxycarbamide group and placebo group in the mean annual crisis rate (all crises), mean difference -2.80 (95% CI -4.74 to -0.86) ($p = 0.005$), and for crises requiring hospitalisation, mean difference -1.50 (95% CI -2.58 to -0.42) ($p = 0.007$).
The study also showed an increase in median time from the initiation of treatment to first painful crisis (2.76 months in the hydroxycarbamide arm compared with 1.35 months on placebo ($p = 0.014$), second painful crisis (6.58 months in the hydroxycarbamide group compared with 4.13 months on placebo ($p < 0.0024$), and third painful crisis (11.9 months in the hydroxycarbamide group compared with 7.04 months on placebo ($p = 0.0002$).

Also rates of acute chest syndrome were decreased in those taking hydroxycarbamide when compared with those taking placebo; RR 0.44 (95% CI 0.28 to 0.68) ($p < 0.001$). Similar decreases were seen in blood transfusion rates, a surrogate for life-threatening illness. Hydroxycarbamide did not reduce rates of hepatic or splenic sequestration when compared with placebo.

In keeping with the mechanism of action of hydroxycarbamide, the MSH study also showed a statistically significant increase in HbF (mean difference 3.9% (95% CI 2.69 to 5.11 ($p < 0.0001$)) and haemoglobin levels (mean difference 0.6 g/dL (95% CI 0.28 to 0.92, $p < 0.0014$) and a decrease in haemolytic markers in the groups treated with hydroxycarbamide. The MSH study showed increased haematological toxicity resulting in a dose reduction in the hydroxycarbamide group as compared with placebo, but there were no infections related to neutropenia or bleeding episodes due to thrombocytopenia.

Paediatric population

Cross-over comparison with placebo (Ferster et al 1996)
A randomized cross-over study was conducted in 25 children and young adults (age range: 2 to 22 years) with homozygous sickle cell anaemia and severe clinical manifestations (defined as > 3 vaso- occlusive crises in the year before study entry and/or with previous history of stroke, acute chest syndrome, recurrent crises without a free interval, or splenic sequestration). The primary outcome measure of the study was the number and duration of hospitalisations. Patients were randomly assigned to receive either hydroxycarbamide first for 6 months, followed by placebo for 6 months, or placebo first, followed by hydroxycarbamide for 6 months. Hydroxycarbamide was administered at an initial dose of 20 mg/kg/day. The dose was increased to 25 mg/kg per day if change in HbF was <2% after 2 months. Dose was reduced by 50% for bone marrow toxicity.
The study reported 16 patients out of 22 (73%) did not require any hospitalisation for painful episodes when treated with hydroxycarbamide as compared with only 3 of 22 (14%) when treated with placebo. In addition, there was a reduction in mean hospital stay; 5.3 days in the hydroxycarbamide group and 15.2 days in the placebo group. There were no deaths reported in the study. An increase in HbF and a decrease in absolute neutrophil count were reported in the hydroxycarbamide group. Similarly after six months of treatment, haemoglobin and MCV increased significantly whilst platelet count and white blood cells (WBC) decreased significantly in the hydroxycarbamide group. Results of this study are presented in Tables 2 and 3 below.

Table 2: Number of hospitalisations and number of days in hospital by treatment (both periods combined) (Ferster et al, 1996)

	Hydroxycarbamide (n=22)	**Placebo (n=22)**
Number of hospitalisations		
0	16	3
1	2	13
2	3	2
3	0	3
4	1	0
5	0	1
Number of days in hospital		
0	16	3
1 – 10	2	13
>10	4	6
Range	0-19	0-104

Table 3: Mean haematologic values before and after 6 months of treatment with hydroxycarbamide (Ferster et al, 1996)

	Before Hydroxycarbamide therapy (mean ± SD)	**After Hydroxycarbamide therapy (mean ± SD)**	**P value**
Haemoglobin (Hb) (g/dL)	8.1 ± 0.75	8.5 ± 0.83	Not significant
MCV (fL)	85.2 ± 9.74	95.5 ± 11.57	<0.001
Mean corpuscular haemoglobin concentration (MCHC) (%)	33.0 ± 2.08	32.3 ± 1.12	Not significant
Platelets ($\times 10^9$/L)	443.2 ± 189.1	386.7 ± 144.6	Not significant
WBC ($\times 10^9$/L)	12.47 ± 4.58	8.9 ± 2.51	<0.001
HbF (%)	4.65 ± 4.81	15.34 ± 11.3	<0.001
Reticulocytes (%)	148.6 ± 53.8	102.7 ± 48.5	<0.001

Low fixed dose hydroxycarbamide in children with Sickle Cell Disease (Jain et al 2012)
In a randomised, double-blind, placebo-controlled study conducted in a tertiary hospital in India, 60 children (aged 5- 18 years) with three or more blood transfusions or vaso-occlusive crises requiring hospitalisation per year, were randomised to fixed dose 10 mg/mg per day hydroxycarbamide (n=30) or to a matched placebo (n=30). The primary outcome was the decrease in the frequency of vaso-occlusive crises per patient per year. Secondary outcomes included the decrease in frequency of blood transfusions and hospitalizations, and increase in HbF levels.

After 18 months of treatment, there was a significant difference in the number of vaso-occlusive crises between the hydroxycarbamide group and placebo group, mean difference -9.60 (95% CI -10.86 to -8.34) ($p < 0.00001$). There was also significant difference between the hydroxycarbamide group and placebo groups in the number of blood transfusions, mean difference -1.85 (95% CI -2.18 to -1.52) ($p < 0.00001$), in the number of hospitalisations, mean difference -8.89 (95% CI -10.04 to -7.74) ($p < 0.00001$), and the duration of hospitalisation, mean difference -4.00 days (95% CI -4.87 to -3.13) ($p < 0.00001$). Results are presented in *Table 4*.

The study also showed a statistically significant increase in HbF and Hb levels and a decrease in haemolytic markers in the groups treated with hydroxycarbamide.

Table 4: Comparison of the number of clinical events before and after intervention in the Hydroxycarbamide and placebo groups

	Hydroxycarbamide		**Placebo**			
Number of events / patient / year	Before	After 18 months	Before	After 18 months	P value[1]	P value[2]
Vaso-occlusive crises	12.13 ± 8.56	0.6 ± 1.37	11.46 ± 3.01	10.2 ± 3.24	0.10	<0.001
Blood transfusions	2.43 ± 0.69	0.13 ± 0.43	2.13 ± 0.98	1.98 ± 0.82	0.25	<0.001
Hospitalisations	10.13 ± 6.56	0.70 ± 1.28	9.56 ± 2.91	9.59 ± 2.94		<0.001

[1.] P value is for comparison between hydroxycarbamide and placebo groups at baseline

[2.] P value is for comparison between hydroxycarbamide and placebo groups at 18 months

Efficacy and safety in infants (BABY HUG study)

BABY HUG was a phase III double-blinded, multi-centre, randomised, placebo-controlled study in infants aged 9 – 18 months. Subjects received oral liquid hydroxycarbamide 20 mg/kg/day without escalation, or placebo for two years. Infants were initially monitored every 2 weeks for adverse events and laboratory toxicities until tolerability of the dose was confirmed, then every 4 weeks. Primary study endpoints were splenic function (qualitative uptake on 99mTc spleen scan) and renal function (glomerular filtration rate by 99mTc-DTPA clearance). Additional evaluations included blood counts, HbF, chemistry profiles, spleen function biomarkers, urine osmolality, neurodevelopment, TCD ultrasonography, growth, and mutagenicity. Ninety-six subjects received hydroxycarbamide and 97 placebo; 86% completed the study.

Regarding primary endpoints, 19 of 70 patients had decreased spleen function at exit in the hydroxycarbamide group vs 28 of 74 patients in the placebo group and a difference in the mean increase in DTPA glomerular filtration rate in the hydroxycarbamide group versus the placebo group of 2 mL/min per 1·73 m². Regarding secondary endpoints, the following were observed: 177 events of pain in 62 patients in the hydroxycarbamide group vs 375 events in 75 patients in the placebo group and 24 events of dactylitis in 14 patients in the hydroxycarbamide group vs 123 events in 42 patients in the placebo group. Haemoglobin and foetal haemoglobin increased in the hydroxycarbamide group compared to the placebo group, whereas the white blood-cell count decreased. The difference in the endpoints between groups was not statistically significant. Toxicity included mild-to-moderate neutropenia.

Primary stroke prevention (TWiTCH study)

Transcranial Doppler (TCD) with Transfusions Changing to Hydroxycarbamide (TWiTCH) was an NHLBI-funded Phase III multicenter, randomized clinical study comparing 24 months of standard treatment (monthly blood transfusions) to alternative treatment (hydroxycarbamide) in 121 children aged 4-16 years with Sickle Cell Disease and abnormal TCD velocities (≥ 200 cm/s) who had received at least 12 months of chronic transfusions and did not have severe vasculopathy, documented clinical stroke, or transient ischaemic attack. The primary objective of this study was to examine if hydroxycarbamide could maintain TCD velocities after an initial period of transfusions as effectively as chronic blood transfusions.

Subjects assigned to standard treatment (n = 61) continued to receive monthly blood transfusions to maintain 30% HbS or lower, while those assigned to the alternative treatment (n = 60), after having received blood transfusions for a mean duration of 4.5 years (±2.8), started oral hydroxycarbamide at 20 mg/kg/day, which was escalated to each participant's maximum tolerated dose. This study used a non-inferiority study design with a primary endpoint of TCD velocity at 24 months, controlling for baseline (enrolment) values. The non-inferiority margin was 15 cm/s. At the first scheduled interim analysis, non-inferiority was shown and the sponsor terminated the study. Final model-based TCD velocities were 143 cm/s (95% CI 140-146) in children who received standard transfusions and 138 cm/s (95% CI 135-142) in those who received hydroxycarbamide, with a difference of 4.54 cm/s (95% CI 0.10-8.98). Non-inferiority ($p = 8.82\times10^{-16}$) and post-hoc superiority ($p = 0.023$) were met. There was no difference in life-threatening neurological events between the treatment groups. Iron overload improved more in the hydroxycarbamide than the transfusion arm, with a greater average change in serum ferritin (–1805 versus –38 ng/mL; $p < 0.0001$) and liver iron concentration (average = –1.9 mg/g versus +2.4 mg/g dry weight liver; $p = 0.0011$).

5.2 Pharmacokinetic properties

Absorption

After oral administration hydroxycarbamide is readily absorbed from the gastrointestinal tract. Peak plasma concentrations are reached within 2 hours and by 24 hours the serum concentrations are virtually zero. Bioavailability is complete or nearly complete in cancer patients.
Following oral administration of hydroxycarbamide oral solution in children aged 6 months to 18 years with sickle cell disease, peak plasma concentrations are reached in 0 to 2 hours. Mean peak plasma concentrations and AUCs increase proportionally with increase of dose.

In a comparative bioavailability study in healthy adult volunteers (n=28), 500 mg of hydroxycarbamide oral solution was demonstrated to be bioequivalent to the reference 500 mg capsule, with respect to both the peak concentration and area under the curve. There was a statistically significant reduction in time to peak concentration with hydroxycarbamide oral solution compared to the reference 500 mg capsule (0.5 versus 0.75 hours, $p = 0.0467$), indicating a faster rate of absorption.

In a study of children with Sickle Cell Disease, liquid and capsule formulations resulted in similar area under the curve, peak concentrations, and half-life. The largest difference in the pharmacokinetic profile was a trend towards a shorter time to peak concentration following ingestion of the liquid compared with the capsule, but that difference did not reach statistical significance (0.74 versus 0.97 hours, $p = 0.14$).

Distribution

Hydroxycarbamide distributes rapidly throughout the human body, enters the cerebrospinal fluid, appears in peritoneal fluid and ascites, and concentrates in leukocytes and erythrocytes. The estimated volume of distribution of hydroxycarbamide approximates total body water. The volume of distribution following oral dosing of hydroxycarbamide is approximately equal to total body water: adult values of 0.48 – 0.90 L/kg have been reported, whilst in children a population estimate of 0.7 L/kg has been reported. The extent of protein binding of hydroxycarbamide is unknown.

Biotransformation

It appears that nitroxyl, the corresponding carboxylic acid and nitric oxide are metabolites: Urea has also been shown to be a metabolite of hydroxycarbamide. Hydroxycarbamide at 30, 100 and 300 µM is not metabolised in vitro by cytochrome P450s of human liver microsomes. At concentrations ranging from 10 to 300 µM, hydroxycarbamide does not stimulate the *in vitro* ATPase activity of recombinant human P glycoprotein (P-gp), indicating that hydroxycarbamide is not a P-gp substrate. Hence, no interaction is to be expected in case of concomitant administration with substances being substrates of cytochromes P450 or P-gp.

Elimination

The total body clearance of hydroxycarbamide in adult patients with Sickle Cell Disease is 0.17 L/h/kg.

The respective value in children was similar, 0.22 L/h/kg.
A significant fraction of hydroxycarbamide is eliminated by nonrenal (mainly hepatic) mechanisms. In adults, the urinary recovery of unchanged drug is reported to be approximately 37% of the oral dose when renal function is normal. In children, the fraction of hydroxycarbamide excreted unchanged into the urine comprised about 50%.
In adult cancer patients, hydroxycarbamide was eliminated with a half-life of approximately 2-3 hours. In children with Sickle Cell Disease, the mean half-life was reported to be 3.9 hours.

Elderly
Although there is no evidence of an age effect on the pharmacokinetic-pharmacodynamic relationship, elderly patients may be more sensitive to the effects of hydroxycarbamide and therefore consideration should be given to starting with a lower initial dose and more cautious dose escalation. Close monitoring of blood parameters is advised (see section 4.2).

Renal impairment
As renal excretion is a pathway of elimination, consideration should be given to decreasing the dose of hydroxycarbamide in patients with renal impairment. In an open single-dose study in adult patients with Sickle Cell Disease the influence of renal function on pharmacokinetics of hydroxycarbamide was assessed. Patients with normal (CrCl > 90 ml/min), mild (CrCl 60-89 ml/min), moderate (CrCl 30- 59 ml/min), severe (CrCl 15-29 ml/min) renal impairment, and End Stage Renal Disease (CrCL < 15 ml/min) received hydroxycarbamide as a single dose of 15 mg/kg body weight. In patients, whose CrCl was below 60 ml/min or patients with End Stage Renal Disease the mean exposure to hydroxycarbamide was approximately 64% higher than in patients with normal renal function.
It is recommended that the starting dose is reduced by 50% in patients with CrCl <60 ml/min (see sections 4.2 and 4.3).
Close monitoring of blood parameters is advised in these patients.

Hepatic impairment
There are no data that support specific guidance for dose adjustment in patients with hepatic impairment, but, due to safety considerations, hydroxycarbamide is contraindicated in patients with severe hepatic impairment (see section 4.3). Close monitoring of blood parameters is advised in patients with hepatic impairment.

5.3 Preclinical safety data

Preclinical toxicity studies have demonstrated the most commonly observed effects include bone marrow depression in rats, dogs and monkeys. In some species cardiovascular and haematological effects have also been observed. Observations in monkeys have also shown lymphoid atrophy and degeneration of the small and large intestine. Toxicology studies have also demonstrated testicular atrophy with decreased spermatogenesis and sperm count in rats and decreased testis weight and reduced sperm counts in mice as well. While in dogs reversible spermatogenic arrest was noted.

Hydroxycarbamide is unequivocally genotoxic and although conventional long-term carcinogenicity studies have not been conducted, hydroxycarbamide is presumed to be a transspecies carcinogen which implies a carcinogenic risk to humans.

Hydroxycarbamide crosses the placental barrier, demonstrated by dams exposed to hydroxycarbamide during gestation. Embryotoxicity manifesting as decreased foetal viability, reduced live litter sizes, and developmental delays has been reported in species including mice, hamsters, cats, dogs, and monkeys at doses comparable to human doses. Teratogenic effects manifested as partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, and missing lumbar vertebrae.

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

Overall, exposure to hydroxycarbamide produces abnormalities in several experimental animal species and affects the reproductive capacity of male and female animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Xanthan gum (E415)
Sucralose (E955)
Strawberry flavour
Methyl parahydroxybenzoate (E218)
Sodium hydroxide (E524)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
After first opening: 12 weeks.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

6.5 Nature and contents of container

Amber type III glass bottle with tamper evident child-resistant closure (HDPE with expanded polyethylene liner) containing 150 ml of oral solution.

Each pack contains one bottle, an LDPE bottle adaptor and 2 dosing syringes (a syringe graduated to 3 ml and a syringe graduated to 10 ml).

6.6 Special precautions for disposal and other handling

Safe handling
Anyone handling hydroxycarbamide should wash their hands before and after administering a dose. To decrease the risk of exposure, parents and care givers should wear disposable gloves when handling hydroxycarbamide. To minimise air bubbles, the bottle should not be shaken prior to dosing.

Hydroxycarbamide contact with skin or mucous membrane must be avoided. If hydroxycarbamide comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water. Spillages must be wiped immediately.

Women who are pregnant, planning to be or breast-feeding should not handle hydroxycarbamide.

Parents / care givers and patients should be advised to keep hydroxycarbamide out of the sight and reach of children. Accidental ingestion can be lethal for children.

Keep the bottle tightly closed to protect the integrity of the product and minimise the risk of accidental spillage.

Syringes should be rinsed and washed with cold or warm water and dried completely before the next use. Store syringes in a hygienic place with the medicinal product.

Disposal
Hydroxycarbamide is cytotoxic. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1366/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 July 2019
Date of latest renewal: 16 May 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pronav Clinical Ltd.
Unit 5
Dublin Road Business Park
Carraroe, Sligo
F91 D439
Ireland

Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Xromi 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 to ensure the safe and effective use of the product, to minimise the risks listed below and to reduce the burden of adverse reactions with Xromi.

The MAH shall ensure that in each Member State where Xromi is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Xromi have access to/are provided with the following educational package to be disseminated through professional bodies:
- Physician educational material
- Patient information pack

The physician educational material should contain:
- The Summary of Product Characteristics
- Guide for healthcare professionals

The Guide for healthcare professionals shall contain the following key elements:
- Indication, dosage and dose adjustment;
- Description of safe handling of Xromi, including the risk of medication error due to the use of two different dosing syringes;
- Warnings about important risks associated with using Xromi:
    - Switching patients from capsule and tablet to liquid formulation;
    - Need for contraception;
    - Risk to male and female fertility, potential risk to foetus and breast feeding;
    - Management of adverse drug reactions;

The patient information pack should contain:
- Patient information leaflet
- A patient/carer guide

The Patient/carer guide shall contain the following key elements:
- Indication;
- Instructions for proper and safe use of the product, including clear instructions on the use of two different dosing syringes to avoid the risk of medication error;
    - Need for contraception;
    - Risk to male and female fertility, potential risk to foetus and breast feeding

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xromi 100 mg/ml oral solution
hydroxycarbamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of solution contains 100 mg hydroxycarbamide.

3. LIST OF EXCIPIENTS

Also contains: methyl parahydroxybenzoate (E218). See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution.

Bottle
Bottle adaptor
3 ml and 10 ml dosing syringes.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Take as directed by your doctor using the dosing syringes provided.
Do not shake the bottle.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic: Handle with caution.

8. EXPIRY DATE

EXP:
Discard 12 weeks after first opening.
Open date: _____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1366/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xromi

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Xromi 100 mg/ml oral solution
hydroxycarbamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of solution contains 100 mg hydroxycarbamide.

3. LIST OF EXCIPIENTS

Also contains: methyl parahydroxybenzoate (E218). See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution
150 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Take as directed by your doctor using the dosing syringes provided.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic: Handle with caution.

8. EXPIRY DATE

EXP:
Discard 12 weeks after first opening.
Open date: _____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1366/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Xromi 100 mg/ml oral solution
hydroxycarbamide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xromi is and what it is used for
2. What you need to know before you take Xromi
3. How to take Xromi
4. Possible side effects
5. How to store Xromi
6. Contents of the pack and other information

1. What Xromi is and what it is used for

Xromi contains hydroxycarbamide, a substance which reduces the growth and multiplication of some cells in the bone marrow. These effects lead to a reduction of circulating red, white and coagulation blood cells. In Sickle Cell Disease, hydroxycarbamide also helps to prevent red blood cells from taking the abnormal sickle shape.
Sickle Cell disease is an inherited blood disorder that affects the disc shaped red cells of the blood. Some cells become abnormal, rigid and take a crescent or sickle shape which leads to anaemia. The sickle cells also get stuck in blood vessels, blocking blood flow. This can cause acute pain crises and organ damage.

Xromi is used to prevent the complications of blocked blood vessels caused by Sickle Cell Disease in patients over 9 months of age. Xromi will decrease the number of painful crises as well as the need for hospitalisation as a result of the disease.

2. What you need to know before you take Xromi

Do not take Xromi

- if you are allergic to hydroxycarbamide or any of the other ingredients of Xromi (listed in section 6).
- if you suffer from severe liver disease
- if you suffer from severe kidney disease
- if you have decreased production of red, white, or coagulating blood cells (‘myelosuppressed’) as described in section 3 “How to take Xromi, Treatment follow-up”
- if you are pregnant or breast-feeding (see section “Pregnancy, breast-feeding and fertility”)
- if you take antiretroviral medicines for the treatment of Human Immunodeficiency Virus (HIV), the virus which causes AIDS

Warnings and precautions

Test and checks

Your doctor will run blood tests:
- to check your blood count before and during treatment with Xromi
- to monitor your liver before and during treatment with Xromi
- to monitor your kidneys before and during treatment with Xromi

Talk to your doctor, pharmacist or nurse before taking Xromi
- if you have extreme tiredness, weakness and shortness of breath, which may be symptoms of a lack of red blood cells (anaemia)
- if you have bleeding or bruise easily, which may be symptoms of low levels of cells in the blood known as platelets
- if you have a liver disease (additional monitoring may be needed)
- if you have a kidney disease (the dose may be adjusted)
- if you have leg ulcers
- if you have a known lack of vitamin B_{12} or folate
- if you have previously received radiotherapy or chemotherapy, or are currently taking any other medicines for cancer treatment, especially interferon therapy

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Xromi.

Talk to your doctor immediately during taking Xromi
- if you have tiredness, shortness of breath, unexplained bruising or bleeding, which may be symptoms of secondary leukaemia. Secondary leukaemia has been reported in patients receiving long-term hydroxycarbamide for some types of blood cancers (myeloproliferative disorders, such as polycythaemia).
- if you have ulcers, which may be symptoms of cutaneous vasculitic toxicities. Cutaneous vasculitic toxicities are cutaneous lesions that have been reported in patients with some types of blood cancers (myeloproliferative disorders) during therapy with hydroxycarbamide, most often in patients with a history of, or currently receiving interferon therapy.
- if you have suspicious changes in your skin, such as new spots and changes to existing freckles or moles, which may be symptoms of skin cancer. Skin cancer has been reported in patients receiving long term hydroxycarbamide.
  You should protect your skin from the sun and regularly inspect your skin yourself during the treatment and after discontinuation of the therapy with Xromi. Your doctor will also inspect your skin during routine follow-up visits.
- if you experience persistent ocular symptoms such as redness and pain of the eyes, sensitivity to light, and/or reduced vision while taking hydroxycarbamide, please consult a doctor promptly because these can be indicative of a rare but serious ocular disease called limbal stem cell deficiency. See also section 4.

Children

Do not give this medicine to children from birth to 9 months of age because it is unlikely to be safe.

Other medicines and Xromi

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor, nurse or pharmacist if you are taking any of the following:

- other myelosuppressive medicines (those that decrease production of red, white, or coagulating blood cells)

- radiation therapy or chemotherapy
- any medicines for cancer treatment, especially interferon therapy - when used with Xromi there is a greater chance of side effects, such as anaemia
- antiretroviral medicines (those that inhibit or destroy a retrovirus such as HIV), e.g. didanosine, stavudine, and indinavir (a drop in your white cell count may occur)
- live vaccines, e.g. measles, mumps, rubella (MMR), chicken pox
- continuous glucose monitor (CGM), used to test your blood glucose (hydroxycarbamide may falsely elevate sensor glucose results from certain CGM systems and may lead to hypoglycaemia if sensor glucose results are relied upon to dose insulin).

Pregnancy, breast-feeding and fertility

Do not take Xromi if you are planning to have a baby without first speaking to your doctor for advice. This applies to both men and women. Xromi may harm your sperm or eggs.

Xromi must not be used during pregnancy. Xromi should be stopped 3 to 6 months prior to becoming pregnant, if possible.

Please contact your doctor immediately if you think you may be pregnant.

You and your partner must use effective contraception methods before, during and after your treatment with Xromi. The use of effective contraception methods must be continued after the end of your treatment with Xromi, for at least 6 months for female and 3 months for male patients.

For male patients taking Xromi, if your partner becomes pregnant or plans to become pregnant, your doctor will discuss with you the potential benefits and risks of continuing using Xromi.

Hydroxycarbamide, the active substance of Xromi, passes into human breast milk. Do not breast-feed while taking Xromi. Ask your doctor or pharmacist for advice.

Driving and using machines

Xromi can make you feel drowsy. You should not drive or operate any machinery unless it has been shown not to affect you, and you have discussed it with your doctor.

Xromi contains methyl parahydroxybenzoate (E218)

Xromi contains methyl parahydroxybenzoate (E218) which may cause allergic reactions (possibly delayed).

3. How to take Xromi

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Xromi should only be given to you by a specialist doctor who is experienced in treating blood problems.

- When you take Xromi your doctor will take regular blood tests. This is to check the number and type of cells in your blood and to check your liver and kidney.
- Depending on the dose you take, these tests may be performed initially once a month and then every 2-3 months.
- Depending on these results your doctor may change your dose of Xromi.

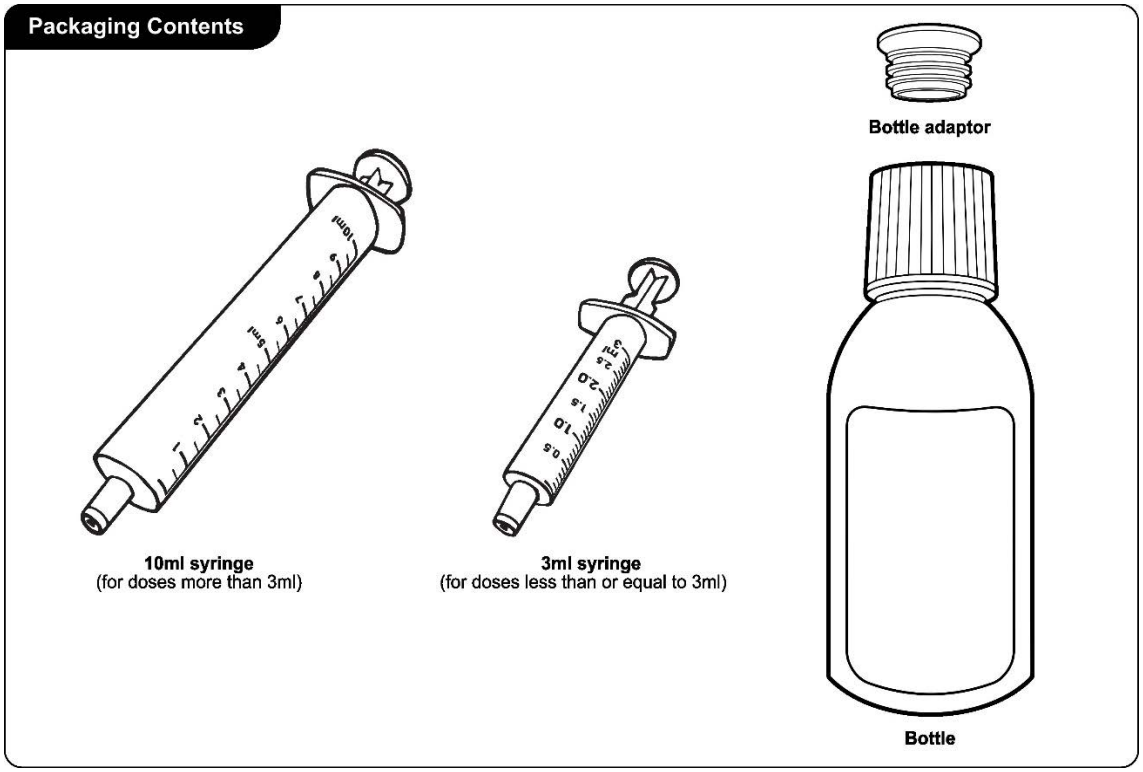
Check with your doctor or pharmacist if you are not sure. The usual starting dose for adults, adolescents and children over the age of 9 months is 15 mg/kg each day and the usual maintenance dose is between 20-25 mg/kg. Your doctor will prescribe the correct dose for you. Sometimes the doctor may change your dose of Xromi, for example as a result of different tests. If you are not sure how much medicine to take, always ask your doctor or nurse.

Xromi with food and drink
You can take this medicine with or after meals at any time of the day. However, the choice of method and time of day should be consistent from day to day.

Use in elderly
You may be more sensitive to the effects of Xromi and your doctor may need to give you a lower dose.

If you have kidney disease
Your doctor may need to give you a lower dose.
You should not take Xromi if you have severe kidney disease.

Handling
Your pack of Xromi contains a bottle of medicine, a cap, a bottle adaptor and two dosing syringes (a 3 ml and a 10 ml syringe). Always use the syringes provided to take your medicine.



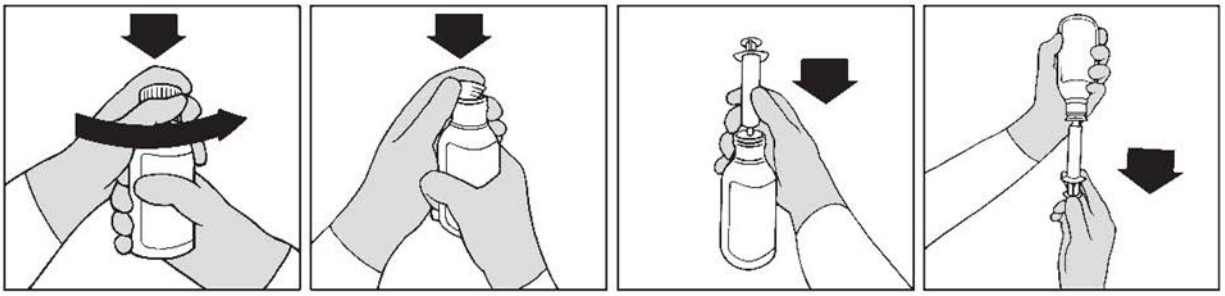
It is important that you use the correct dosing syringe for your medicine. Your doctor or pharmacist will advise which syringe to use depending on the dose that has been prescribed.

The smaller 3 ml syringe, marked from 0.5 ml to 3 ml, is for measuring doses of less than or equal to 3 ml. You should use this one if the total amount you have to take is less than or equal to 3 ml (each graduation of 0.1 ml contains 10 mg of hydroxycarbamide).
The larger 10 ml syringe, marked from 1 ml to 10 ml, is for measuring doses of more than 3 ml. You should use this one if the total amount you have to take is more than 3 ml (each graduation of 0.5 ml contains 50 mg of hydroxycarbamide).

If you are a parent or care giver administering the medicine, wash your hands before and after administering a dose. Wipe up spillages immediately. To decrease the risk of exposure disposable gloves should be used when handling Xromi. To minimise air bubbles, do not shake the bottle before administering a dose.

If Xromi comes into contact with skin, eyes or nose, it should be washed immediately and thoroughly with soap and water.

When you use the medicine follow the instructions below:



1. Put on disposable hand gloves before handling Xromi.
2. Remove the bottle cap **(figure 1)** and push the adaptor firmly into the top of the bottle and leave in place for future doses **(figure 2)**.
3. Push the tip of the dosing syringe into the hole in the adaptor **(figure 3)**. **Your doctor or pharmacist will advise you of the correct syringe to use, either the 3 ml or the 10 ml syringe in order to give the correct dose**.
4. Turn the bottle upside down **(figure 4)**.
5. Pull the plunger of the syringe back so that the medicine is drawn from the bottle into the syringe. Pull the plunger back to the point on the scale that corresponds to the dose prescribed **(figure 4)**. If you are not sure about how much medicine to draw into the syringe, always ask your doctor or nurse for advice.
6. Turn the bottle back the right way up and carefully remove the syringe from the adaptor, holding it by the barrel rather than the plunger.
7. Gently put the tip of the syringe into your mouth and to the inside of your cheek.
8. Slowly and gently push the plunger down to gently squirt the medicine into the inside of your cheek and swallow it. DO NOT forcefully push down the plunger, or squirt the medicine to the back of your mouth or throat, as you may choke.
9. Remove the syringe from your mouth.
10. Swallow the dose of oral solution then drink some water, making sure no medicine is left in your mouth.
11. Put the cap back on the bottle with the adaptor left in place. Ensure that the cap is tightly closed.
12. Wash the syringe with cold or warm tap water and rinse well. Hold the syringe under water and move the plunger up and down several times to make sure the inside of the syringe is clean. Let the syringe dry completely before you use that syringe again for dosing. Store the syringe in a hygienic place with the medicine.

Repeat the above for each dose as instructed by your doctor or pharmacist.

If you take more Xromi than you should

If you take more Xromi than you should, tell your doctor or go to a hospital immediately. Take the medicine pack and this leaflet with you. The most common symptoms of overdose with Xromi are:
- Redness of the skin,
- Soreness (touch is painful) and swelling of the palms of hands and soles of feet followed by the hands and feet becoming scaly,
- Skin becoming strongly pigmented (locally changes of colour),

- Soreness or swelling in the mouth.

If you forget to take Xromi

Tell your doctor. **Do not take a double dose to make up for a forgotten dose.**

If you stop taking Xromi

Do not stop taking your medicine unless advised by your doctor. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any of the following serious side effects, talk to your doctor or go to hospital immediately:

Very common (may affect more than 1 in 10 people):

- A severe infection
- Fever or chills
- Tiredness and/or looking pale

Common (may affect up to 1 in 10 people):

- Unexplained bruising (accumulation of blood under the skin) or bleeding
- Sore (open skin infection) on your skin

Uncommon (may affect up to 1 in 100 people):

- Any yellowing of the whites of the eyes or skin (jaundice)

Rare (may affect up to 1 in 1000 people):

- Ulcers or wounds on your legs

Very rare (may affect up to 1 in 10,000 people):

- Inflammation of the skin causing red scaly patches and possibly occurring together with pain in the joints

Other side effects which are not mentioned above are listed below. Speak to your doctor if you are concerned by any of these side effects.

Very common (may affect more than 1 in 10 people):

- Absence or low amount of sperm in the semen (azoospermia or oligospermia).

Common (may affect up to 1 in 10 people):

- Nausea
- Headache
- Dizziness
- Constipation
- Darkening of the skin, nails and mouth

- Dry skin
- Hair loss

Uncommon (may affect up to 1 in 100 people):

- Itching red eruption of the skin (rash)
- Diarrhoea
- Vomiting
- Inflammation or ulceration of the mouth
- Elevated liver enzymes

Other side effects (the frequency is not known):

- Isolated cases of malignant disease of blood cells (leukaemia)
- Skin cancers in elderly patients
- Stomach pain or heartburn
- Gastrointestinal ulcer
- Fever
- Absence of menstrual cycles (amenorrhoea)
- Weight gain
- Low Vitamin D level in blood test
- Low magnesium level in blood test
- Bleeding
- Eye disease causing redness and pain of the eyes, sensitivity to light, and/or reduced vision (limbal stem cell deficiency). See also section 2.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Xromi

- Keep this medicine out of the sight and reach of children. Accidental ingestion can be lethal for children.
- Do not use this medicine after the expiry date which is stated on the carton and the bottle after 'EXP'. The expiry date refers to the last day of that month.
- After first opening of the bottle, discard any unused contents after 12 weeks.
- Store in a refrigerator (2 °C – 8 °C).
- Keep the bottle tightly closed to prevent spoilage of the medicine and reduce the risk of accidental spillage.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Xromi contains

The active substance is hydroxycarbamide. One ml of solution contains 100 mg of hydroxycarbamide.

The other ingredients are xanthan gum, sucralose (E955), strawberry flavour, methyl parahydroxybenzoate (E218), sodium hydroxide, and purified water. See section 2 “Xromi contains methyl parahydroxybenzoate”.

What Xromi looks like and contents of the pack

Xromi is a clear, colourless to pale yellow, oral solution. It comes in glass bottles of 150 ml capped with a child-resistant closure. Each pack contains one bottle, a bottle adaptor and two dosing syringes (a syringe graduated to 3 ml and a syringe graduated to 10 ml).
Your doctor or pharmacist will advise which syringe to use depending on the dose that has been prescribed.

Marketing Authorisation Holder and Manufacturer
Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany

Manufacturer
Pronav Clinical Ltd.
Unit 5
Dublin Road Business Park
Carraroe, Sligo
F91 D439
Ireland

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for hydroxycarbamide (for centrally authorised product only), the scientific conclusions of PRAC are as follows:

In view of available data on limbal stem cell deficiency risk from the literature, spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between hydroxycarbamide and limbal stem cell deficiency is at least a reasonable possibility. The PRAC concluded that the product information of products containing hydroxycarbamide should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for hydroxycarbamide (for centrally authorised product only) the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing hydroxycarbamide (for centrally authorised product only) is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.