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).

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).

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
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 HPRA Pharmacovigilance Website: www.hpra.ie.

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 m^2. 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

<u>Absorption</u>
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

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