ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Siklos 100 mg film-coated tablet.
Siklos 1 000 mg film-coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Siklos 100 mg film-coated tablet
Each film-coated tablet contains 100 mg of hydroxycarbamide.

Siklos 1 000 mg film-coated tablet
Each film-coated tablet contains 1 000 mg of hydroxycarbamide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Siklos 100 mg film-coated tablet
Off-white oblong-shaped, film-coated tablet with half-scoring on both sides.
The tablet can be divided into two equal parts. Each half of tablet is embossed "H" on one side.

Siklos 1 000 mg film-coated tablet
Off-white, capsule-shaped, film-coated tablet with triple scoring on both sides.
The tablet can be divided into four equal parts. Each quarter of tablet is embossed "T" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Siklos is indicated for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in adults, adolescents and children older than 2 years suffering from symptomatic sickle cell syndrome (see section 5.1).

4.2 Posology and method of administration

Treatment with Siklos should be initiated by a physician experienced in the management of patients with sickle cell syndrome.

Posology

In adults, adolescents and children older than 2 years
The posology should be based on the patient's body weight (b.w.).
The starting dose of hydroxycarbamide is 15 mg/kg b.w. and the usual dose is between 15 and 30 mg/kg b.w./day.
As long as the patient responds to therapy either clinically or haematologically (e.g. increase in haemoglobin F (HbF), Mean Corpuscular Volume (MCV), decrease in neutrophil count), the dose of Siklos should be maintained.
In case of non-response (re-occurrence of crises or lack of reduction in crisis rate), the daily dose may be increased by steps of 2.5 to 5 mg/kg b.w./day using the most appropriate strength.
Under exceptional circumstances a maximum dose of 35 mg/kg b.w./day may be justified under close haematological monitoring (see section 4.4).

If the patient does not respond to the maximum dose of hydroxycarbamide (35 mg/kg b.w./day) given over three to six months, permanent discontinuation of Siklos should be considered.

If blood counts are within the toxic range, Siklos should be temporarily discontinued until blood counts recover. Haematological recovery usually occurs within two weeks. Treatment may then be reinstated at a reduced dose. The dose of Siklos may then be increased again under close haematological monitoring. A dose producing haematological toxicity should not be tried more than two times.

The toxic range may be characterised by the following results of blood tests:

Neutrophils	< 1 500/mm^3
Platelets	< 80 000/mm^3
Haemoglobin	< 4.5 g/dL
Reticulocytes	< 80 000/mm^3 if the haemoglobin concentration < 9 g/dL

Long-term data on the continued use of hydroxycarbamide in patients with sickle cell syndrome are available in children and adolescents, with a follow-up of 12 years in children and adolescents and over 13 years in adults. It is currently unknown how long patients should be treated with Siklos. The duration of treatment is the responsibility of the prescribing physician and should be based on the clinical and haematological status of each patient.

Special populations

Children less than 2 years of age
The safety and efficacy of hydroxycarbamide in children from birth up to 2 years have not yet been established. Limited data suggest that 20 mg/kg/d reduced painful episodes and were safe in children less than 2 years of age but safety of long-term treatment remains to be established. Therefore no recommendation on a posology can be made.

Renal impairment
As renal excretion is a main pathway of elimination, a dose reduction of Siklos should be considered in patients with renal impairment. In patients with creatinine clearance ≤ 60 mL/min, the initial Siklos dose should be decreased by 50%. Close monitoring of blood parameters is advised in these patients. Siklos must not be administered to patients with severe renal impairment (creatinine clearance < 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, Siklos is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 4.4).

Method of administration

Conforming to the individual prescribed dose, the tablet or the half or quarter of the tablet should be taken once daily, preferably in the morning before breakfast and, when necessary, with a glass of water or a very small amount of food.

For patients who are not able to swallow the tablets, these can be disintegrated **immediately before use** in a small quantity of water in a teaspoon. Adding a drop of syrup or mixing with food can mask a possible bitter taste.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Severe hepatic impairment (Child-Pugh classification C).

Severe renal impairment (creatinine clearance < 30 mL/min).

Toxic ranges of myelosuppression as described in section 4.2.

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Bone marrow depression
Treatment with Siklos requires close clinical monitoring. The haematological status of the patient, as well as renal and hepatic functions should be determined prior to, and repeatedly during treatment. During treatment with Siklos, blood counts must be monitored once a month at treatment initiation (i.e. for the first two months) and if the daily dose of hydroxycarbamide is up to 35 mg/kg b.w. Patients who are stable on lower doses should be monitored every 2 months.

Treatment with Siklos should be discontinued if bone marrow function is markedly depressed. Neutropenia is generally the first and most common manifestation of haematological suppression. Thrombocytopenia and anaemia occur less frequently, and are rarely seen without preceding neutropenia. Recovery from myelosuppression is usually rapid when therapy is discontinued. Siklos therapy can then be re-initiated at a lower dose (see section 4.2).

Renal and hepatic impairment
Siklos should be used with caution in patients with mild to moderate renal impairment (see section 4.2).
Since there are limited data in patients with mild to moderate liver impairment, Siklos should be used with caution (see section 4.2).

Leg ulcers and cutaneous vasculitis toxicities
In patients with leg ulcers, Siklos should be used with caution. Leg ulcers are a common complication of sickle cell syndrome, but have also been reported in patients treated with hydroxycarbamide. 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. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease, hydroxycarbamide should be discontinued and/or its dose reduced if cutaneous vasculitic ulcerations develop. Rarely, ulcers are caused by leukocytoclastic vasculitis.

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.

Macrocytosis
Hydroxycarbamide causes macrocytosis, which may mask the incidental development of folic acid and vitamin B_{12} deficiency. Prophylactic administration of folic acid is recommended.

Carcinogenicity
Hydroxycarbamide is unequivocally genotoxic in a wide range of test systems. Hydroxycarbamide is presumed to be a transspecies carcinogen. In patients receiving long-term hydroxycarbamide for myeloproliferative disorders, secondary leukaemia has been reported. It is unknown whether this leukaemogenic effect is secondary to hydroxycarbamide or is associated with the patient's underlying disease. Skin cancer has also been reported in patients receiving long-term hydroxycarbamide.

Safe administration and monitoring

Patients and/or parents or the legal responsible person must be able to follow directions regarding the administration of this medicinal product, their monitoring and care.

4.5 Interaction with other medicinal products and other forms of interaction

Specific interaction studies have not been performed with hydroxycarbamide.

Potentially fatal pancreatitis and hepatotoxicity, and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxycarbamide in combination with first generation antiretroviral medicinal products, particularly didanosine plus stavudine. Patients treated with hydroxycarbamide in combination with didanosine, stavudine, and indinavir showed a median decline in CD4 cells of approximately 100/mm^3.

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.

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 Siklos and concomitant immunisation with live virus vaccines should only be performed if benefits clearly outweigh potential risks.

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
Women of childbearing age receiving hydroxycarbamide should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur.
An effective method of contraception is strongly recommended in women of childbearing potential.
Male and female patients on hydroxycarbamide wishing to conceive should stop treatment 3 to 6 months before pregnancy if possible. The evaluation of the risk-benefit ratio should be made on an individual basis taking into consideration the respective risk of hydroxycarbamide therapy against the switch to a blood transfusion programme.

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. Siklos is not recommended during pregnancy.

The patient should be instructed to immediately contact a doctor in case of suspected pregnancy.

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

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 was observed in male rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Siklos 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 Siklos.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of hydroxycarbamide in sickle cell syndrome was established from clinical trials and confirmed with long-term cohort studies including up to 1 903 adults and children of more than 2 years of age.

The most frequently reported adverse reaction is myelosuppression with neutropenia as the most common manifestation. Bone marrow depression is the dose-limiting toxic effect of hydroxycarbamide. When the maximum tolerated dose is not reached, transient myelotoxicity usually occurs in less than 10% of patients, while under the maximum tolerated dose more than 50% can experience reversible bone marrow suppression. These adverse reactions are expected based on the pharmacology of hydroxycarbamide. Gradual dose titration may help diminish these effects (see section 4.2).

The clinical data obtained in patients with sickle cell syndrome have not shown evidence of adverse reactions of hydroxycarbamide on hepatic and renal function.

Tabulated list of adverse reactions

The adverse reactions are listed below by system organ class and absolute frequency. Frequencies are defined as 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), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness:

Neoplasms, benign, malignant and unspecified:		
	Not known:	Leukaemia and in elderly patients, skin cancers
Blood and lymphatic system disorders:		
	Very common:	Bone marrow depression[1] including neutropenia (< 1.5 x 10^9/L), reticulocytopenia (< 80 x 10^9/L), macrocytosis[2]
	Common:	Thrombocytopenia (< 80 x 10^9/L), anaemia (haemoglobin < 4.5 g/dL)[3]
Nervous system disorders:		
	Common:	Headache
	Uncommon:	Dizziness
Eye disorders:		
	Not known:	Limbal stem cell deficiency
Vascular disorders:		
	Not known:	Bleeding
Gastrointestinal disorders:		
	Uncommon:	Nausea
	Not known:	Gastrointestinal disturbances, vomiting, gastrointestinal ulcer, severe hypomagnesaemia
Hepatobiliary disorders:		
	Rare:	Elevated liver enzymes

Skin and subcutaneous tissue disorders:		
	Common	Skin reactions (for example oral, ungual and cutaneous pigmentation) and oral mucositis.
	Uncommon:	Rash, melanonychia, alopecia
	Rare:	Leg ulcers
	Very rare:	Systemic and cutaneous lupus erythematous
	Not known:	Cutaneous dryness
Reproductive system and breast disorders:		
	Very common:	Oligospermia, azoospermia[4]
	Not known:	Amenorrhea
General disorders and administration site conditions:		
	Not known:	Fever
Investigations:		
	Not known:	Weight gain[5]

[1] Haematological recovery usually occurs within two weeks of withdrawal of hydroxycarbamide.
[2] The macrocytosis caused by hydroxycarbamide is not vitamin B_{12} or folic acid dependent.
[3] Mainly due to infection with Parvovirus, splenic or hepatic sequestration, renal impairment.
[4] Oligospermia and azoospermia 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.
[5] Weight gain may be an effect of improved general conditions.

Pediatric population
Frequency, type and severity of adverse reactions in children is generally similar to adults. Postmarketing data from one observational study with Siklos® (Escort HU) on 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.

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

Acute mucocutaneous toxicity has been reported in patients receiving hydroxycarbamide at doses several times above the therapeutic dose. Soreness, violet erythema, oedema on palms and soles followed by scaling of hand and feet, severe generalised hyperpigmentation of the skin and stomatitis have been observed.

In patients with sickle cell syndrome, 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 b.w./day). It is recommended that blood counts are monitored for several weeks after overdose since recovery may be delayed.

Treatment of overdose consists of gastric lavage, followed by symptomatic treatment and control of bone marrow function.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

All mechanisms of action of hydroxycarbamide are not fully understood. One of the mechanisms is the increase in foetal haemoglobin (HbF) concentrations in sickle cell patients. HbF interferes with the polymerisation of HbS and thus impedes the sickling of red blood cell and in turn decreases vasocclusion and haemolysis. In all clinical studies, there was a significant increase in HbF from baseline after hydroxycarbamide use. Increased HbF also increases red blood cell survival and total haemoglobin level and thus reduces anaemia in these patients.

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 syndrome include decrease in neutrophils, increase in water content of red blood cells, increased deformability of sickled cells, and altered adhesion of red blood cells to the endothelium.

In addition hydroxycarbamide causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or protein.

Pharmacodynamic effects

Beside the inconstant correlation between reduction of crisis rate and the increase in HbF, the cytoreductive effect of hydroxycarbamide, particularly the decrease in neutrophils, was the factor with the strongest correlation with the reduction in crisis rate.

Clinical efficacy and safety

In nearly all clinical studies conducted in sickle cell syndrome, hydroxycarbamide reduced the frequency of vaso-occlusive episodes by 40% to 80%, in children and in adults. The same decrease was observed for the number of hospital admissions and the number of days of hospitalisation in the treated groups. The yearly frequency of acute chest syndrome (ACS) was also reduced by 25 to 68% under hydroxycarbamide in several studies. Acute chest syndrome is a frequent life-threatening complication of sickle cell syndrome and is characterised by chest pain or fever or dyspnoea with recent infiltrate on chest X-ray.
A sustained clinical benefit was demonstrated in patients remaining on hydroxycarbamide treatment for more than 8 years.

In 1 906 patients included in the cohort study ESCORT HU, after twelve and twenty-four months of treatment with hydroxycarbamide and compared to the baseline, it was observed a significant increase of Hb level (+1.4 g/dL and 1.5 g/dL) and percentage of HbF (+14.65% and 15%). In parallel after one year of treatment there was a significant reduction of the number of painful crises lasting >48 h (-40% in children and -50% in adults), episodes of ACS (-68% in children and -57% in adults), and hospitalizations (-44% in children and -45% in adults) and the percentage of patients requiring blood transfusion decreased by 50% The safety profile of hydroxycarbamide in adults and in children observed in ESCORT-HU was consistent with previous published data with no new risk (Montalembert 2021).

Paediatric population

In NOHARM trial (Opoka 2017) children of mean age of 2.2 years old (from 1 to 3.99 years) were randomized to either hydroxycarbamide (n=104) or placebo (n=104). Treatment was administered once daily at 20 ± 2.5 mg/kg for 12 months. A composite SCD-related clinical outcome (vaso-occlusive painful crisis, dactylitis, acute chest syndrome, splenic sequestration, or blood transfusion) was less frequent with hydroxyurea (45%) than placebo (69%, p=0.001). Regarding the risk of increased infection in children with drug-induced neutropenia, it was rare in NOHARM and did not differ on hydroxyurea versus placebo treatment.

At the end of the NOHARM trial, children were enrolled in the NOHARM extension trial (John 2020), and randomly assigned in a 1:1 ratio either to receive hydroxycarbamide at a fixed standard dose (mean [±SD], 20±5 mg per kilogram per day) or to escalate hydroxycarbamide to the maximum tolerated dose. 187 children were randomized: 94 (age 4.6 ± 1.0) in the fixed dose group (19.2±1.8 mg /kg/d) and 93 (age 4.8 ± 0.9) in the dose escalation group (29.5±3.6 mg/kg/d). After 18 months, an increase in Hb level (+0.3 g/dL) and % HbF (+8%) was found in the escalation group.
Clinical adverse events of any grade were more frequent in the fixed-dose group, including all sickle cell–related events (245 vs 105) and specific events: vaso-occlusive pain crisis (200 vs 86) and acute chest syndrome or pneumonia (30 vs 8). The number of key medical interventions were also fewer in the dose-escalation group than in the fixed-dose group, both for transfusions (34 vs. 116) and hospitalizations (19 vs. 90).

In infants with SS/Sb0 aged 9–23 months, a decrease of episodes of pain (-52%, 177 events vs 375), dactylitis (- 80%, 24 vs 123), acute chest syndrome (8 vs 27) and hospitalizations (- 28%, 232 vs 324) has been reported with hydroxycarbamide (n=96) compared to placebo (n=97) respectively in the randomized controlled trial Baby Hug. In 25 patients treated for 1 year in the uncontrolled ESCORT HU over 1 year, compared to 1 year prior to enrolment (n=25), reduction of vaso-occlusive crises: -42% and hospitalizations: -55%.
The benefit risk ratio and long-term safety remain to be established in this population.

In the uncontrolled cohort ESCORT HU, a subset of 27 pediatric patients with severe chronic anemia, treated with Siklos for 12 months, had haemoglobin levels less than 7 g/dL at baseline. Of these, only 6 (22%) patients had levels less than 7 g/dL at Month 12. While there have been a majority of patients (56%) who had a change from baseline equal to or exceeding 1 g/dL, due to the large proportion of missing data, potential for regression to the mean and that an effect of transfusions could not be excluded, no robust efficacy conclusions can be made from this uncontrolled study.

5.2 Pharmacokinetic properties

Absorption
After oral administration of 20 mg/kg of hydroxycarbamide, a rapid absorption is observed with peak plasma levels of about 30 mg/L occurring after 0.75 and 1.2 h in children and adult patients with sickle cell syndrome, respectively. The total exposure up to 24 h post-dose is 124 mg.h/L in children and adolescents and 135 mg.h/L in adult patients. The oral bioavailability of hydroxycarbamide is almost complete as assessed in indications other than sickle cell syndrome.

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 at steady state adjusted for bioavailability is 0.57 L/kg in patients with sickle cell syndrome (amounting to approximately 72 and 90 L in children and adults, respectively). The extent of protein binding of hydroxycarbamide is unknown.

Biotransformation
The biotransformation pathways as well as the metabolites are not fully characterised. Urea is one 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 (PGP), indicating that hydroxycarbamide is not a PGP substrate. Hence, no interaction is to be expected in case of concomitant administration with substances being substrates of cytochromes P450 or P-glycoprotein.

Elimination
In a repeated dose study in adult patients with sickle cell syndrome approximately 60% of the hydroxycarbamide dose was detected in urine at steady state. In adults, the total clearance adjusted for bioavailability was 9.89 L/h (0.16 L/h/kg) thereof 5.64 and 4.25 L/h by renal and non-renal clearance, respectively. The respective value for total clearance in children was 7.25 L/h (0.20 L/h/kg) with 2.91 and 4.34 L/h by renal and non-renal pathways.
In adults with sickle cell syndrome, mean cumulative urinary hydroxycarbamide excretion was 62% of the administered dose at 8 hours, and thus higher than in cancer patients (35–40%). In patients with sickle cell syndrome hydroxycarbamide was eliminated with a half-life of approximately six to seven hours, which is longer than reported in other indications.

Geriatric, gender, race
No information is available regarding pharmacokinetic differences due to age (except paediatric patients), gender or race.

Paediatric population
In paediatric and adult patients with sickle cell syndrome the systemic exposure to hydroxycarbamide at steady state was similar by means of the area under the curve. The maximum plasma levels and the apparent volume of distribution related to body weight were well comparable between age groups. The time to reach maximum plasma concentration and the percentage of the dose excreted in urine were increased in children compared to adults. In paediatric patients, the half-life was slightly longer and the total clearance related to body weight slightly higher than in adult patients (see section 4.2).

Renal impairment
As renal excretion is a pathway of elimination, consideration should be given to decreasing the dose of Siklos in patients with renal impairment. In an open single-dose study in adult patients with sickle cell syndrome (*Yan JH et al, 2005*) the influence of renal function on pharmacokinetics of hydroxycarbamide was assessed. Patients with normal (creatinine clearance CrCl>80 mL/min), mild (CrCl 60–80 mL/min), moderate (CrCl 30 - 60 mL/min), or severe (<30 mL/min) renal impairment received hydroxycarbamide as a single dose of 15 mg/kg b.w. by using 200 mg, 300 mg, or 400 mg capsules. 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. As evaluated in a further study, in patients with a CrCl<60 mL/min the area under the curve was approximately 51% higher than in patients with a CrCl ≥60 mL/min, which suggests that a dose reduction of hydroxycarbamide by 50% may be appropriate in patients with a CrCl ≤ 60 mL/min. Haemodialysis reduced the exposure to hydroxycarbamide by 33% (see sections 4.2 and 4.4).
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, Siklos 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

In preclinical toxicity studies the most common effects noted included bone marrow depression, lymphoid atrophy and degenerative changes in the epithelium of the small and large intestines. Cardiovascular effects and haematological changes were observed in some species. Also, in rats testicular atrophy with decreased spermatogenesis occurred, while in dogs reversible spermatogenic arrest was noted.

Hydroxycarbamide is unequivocally genotoxic in a wide range of test systems.
Conventional long-term studies to evaluate the carcinogenic potential of hydroxycarbamide have not been performed. However, hydroxycarbamide is presumed to be a transspecies carcinogen.

Hydroxycarbamide crosses the placenta barrier and has been demonstrated to be a potent teratogen and embryotoxic in a wide variety of animal models at or below the human therapeutic dose. Teratogenicity was characterised by partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae. Embryotoxicity was characterized by decreased foetal viability, reduced live litter sizes, and developmental delays.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium stearyl fumarate
Silicified microcrystalline cellulose
Basic butylated methacrylate copolymer

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

In-use
Unused broken tablets must be replaced in the bottle and must be used within three months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with polypropylene child-resistant closure with a dessicant unit.

Siklos 100 mg film-coated tablet
Pack sizes of 60, 90 or 120 tablets.
Not all pack sizes may be marketed.

Siklos 1 000 mg film-coated tablet
Pack size of 30 tablets.

6.6 Special precautions for disposal and other handling

Siklos is a medicinal product that must be handled with care. People who are not taking Siklos and in particular pregnant women should avoid being in contact with hydroxycarbamide.
Anyone handling Siklos should wash their hands before and after contact with the tablets.
Any unused product or waste material should be disposed of in accordance with local requirements.

In case the prescribed dose requires breaking the tablet in halves or quarters, this should be done out of the reach of food. Powder eventually spilled from the broken tablet should be wiped up with a damp disposable towel, which must be discarded.

7. MARKETING AUTHORISATION HOLDER

THERAVIA
16 Rue Montrosier
92200 Neuilly-sur-Seine
France
Phone: +33 1 72 69 01 86
Fax: +33 1 73 72 94 13
E-mail : question@theravia.com

8. MARKETING AUTHORISATION NUMBER(S)

Siklos 100 mg film-coated tablet
EU/1/07/397/002
EU/1/07/397/003
EU/1/07/397/004

Siklos 1 000 mg film-coated tablet
EU/1/07/397/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29/06/2007
Date of latest renewal: 24/04/2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://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

Delpharm Lille
Parc d'Activités Roubaix-Est
22 rue de Toufflers
CS 50070
59452 Lys-lez-Lannoy
France

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 autorisation 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe Siklos are provided with a physician information pack containing the following:

- Treatment guide for physicians
- Patient treatment guide
- Dosing sheet (in countries where both strengths are available)

The treatment guide for physicians should contain the following key elements:

- The Summary of Product Characteristics
- Need for contraception
- Risk to male and female fertility, potential risk to foetus and breast feedingManagement of adverse drug reactions
- Risk of medication error due to the availability of two different strengths (where both strengths are available)

The treatment guide for the patient should contain the following key elements:

- Package leaflet
- Handling of broken tablets
- Need for contraception
- Risk to male and female fertility, potential risk to foetus and breast feeding
- Risk of medication error due to the availability of two different strengths (where both strengths are available)

If necessary, pharmacists should receive targeted communication on the risk of medication error due to the confusion between the two strengths where both are available.

The MAH must implement this educational plan nationally, and as agreed with the competent authorities in the Member States

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Siklos 100 mg film-coated tablet
hydroxycarbamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of hydroxycarbamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 tablets
90 tablets
120 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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 tablets with caution.

8. EXPIRY DATE

EXP:
In-use shelf life of broken tablets: 3 months.

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

THERAVIA, 16 Rue Montrosier, 92200 Neuilly-sur-Seine, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/397/002 60 tablets
EU/1/07/397/003 90 tablets
EU/1/07/397/004 120 tablets

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

siklos 100 mg

17. UNIQUE IDENTIFIER- 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER- HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Siklos 100 mg tablet
hydroxycarbamide
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 tablets
90 tablets
120 tablets

6. OTHER

Cytotoxic

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Siklos 1 000 mg film-coated tablet
hydroxycarbamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 000 mg of hydroxycarbamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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 tablets with caution.

8. EXPIRY DATE

EXP:
In-use shelf life of broken tablets: 3 months.

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

THERAVIA, 16 Rue Montrosier, 92200 Neuilly-sur-Seine, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/397/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

siklos 1 000 mg

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

1. NAME OF THE MEDICINAL PRODUCT

Siklos 1 000 mg tablet
hydroxycarbamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 000 mg of hydroxycarbamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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 tablets with caution.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

THERAVIA

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/397/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: information for the user

Siklos 100 mg film-coated tablet
Siklos 1 000 mg film-coated tablet
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, or 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, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Siklos is and what it is used for

Siklos is used to prevent painful crises, including sudden chest pain, caused by sickle cell disease, in adults, adolescents and children older than 2 years.

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 anemia. The sickle cells also get stuck in blood vessels, blocking blood flow. This can cause acute pain crises and organ damage.

For severe painful crises, most patients require hospitalisation. Siklos will decrease the number of painful crises as well as the need for hospitalisation linked with the disease.

The active substance of Siklos, hydroxycarbamide, is a substance which inhibits growth and proliferation of some cells, such as blood cells. These effects lead to a reduction of circulating red, white and coagulation blood cells (myelosuppressive effect). In sickle cell disease, hydroxycarbamide helps also to prevent red blood cells from taking abnormal shape.

2. What you need to know before you take Siklos

Do not take Siklos
- if you are allergic to hydroxycarbamide or any of the other ingredients of this medicine (listed in section 6),
- if you suffer from severe liver disease,
- if you suffer from severe kidney disease,
- if you are myelosuppressed (if you have decreased production of red, white, or coagulating blood cells) as described in section 3 “How to take Siklos, Treatment follow-up”,
- if you are breast-feeding (see section “Pregnancy, breast-feeding and fertility”).

Warnings and precautions

Talk to your doctor or pharmacist or nurse before taking Siklos

- if you have a liver disease,
- if you have a kidney disease,
- if you have leg ulcers,
- if you are taking other myelosuppressive medicines (decrease production of red, white, or coagulating blood cells) or receiving radiation therapy,
- if you have a known lack of vitamin B_{12} or folate.

If you experience (or have experienced) any of the above, please tell your doctor. If you have any question, please ask your doctor or pharmacist or nurse.

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.

Patients and/or parents or the legal responsible person must be able to follow directions regarding the administration of this medicine, their monitoring and care.

Other medicines and Siklos

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Information sharing is especially required for
- some 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),
- myelosuppressive medicines (those that decrease production of red, white, or coagulating blood cells) and radiation therapy,
- some vaccines,
- 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

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Siklos is not recommended during pregnancy. Please contact your doctor immediately if you think you may be pregnant. The use of effective contraception is strongly recommended.

If you become pregnant or plan to become pregnant while taking Siklos, your doctor will discuss with you the potential benefits and risks of continuing using Siklos.

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

The active substance of Siklos passes into human breast-milk. You must not breast-feed while taking Siklos.

Hydroxycarbamide may decrease sperm production in male patients while they are being treated.

Driving and using machines

Some people may experience dizziness when using Siklos. Do not drive or use any tools or machines if you experience dizziness whilst taking Siklos.

3. How to take Siklos

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

Dose

Your doctor will tell you how much of Siklos to take each day and will describe the dose in whole, half or quarter tablets.

The prescribed dose of Siklos must be taken once daily, preferably in the morning before breakfast.
It can be taken with a glass of water or a very small amount of food.
If you cannot swallow the tablets, you can disintegrate them in water **immediately before use**:

- Place the required dose (preferably broken if Siklos 1 000 mg tablet is used) in a teaspoon and add some water.
- As soon as the tablet is disintegrated, swallow the content of the teaspoon. You can add a drop of syrup or mix the content with food to mask a possible bitter taste.
- Then drink a large glass of water or any other drink.

Handling

Siklos is a cytotoxic medicine that must be handled with care.
Any person, in particular pregnant women, who are not taking Siklos should avoid direct contact with the parts when breaking a tablet. Wash your hands before and after contact with the tablets.
In case the prescribed dose requires breaking the tablet in halves or quarters, this should be done out of the reach of food. Powder spilled from the broken tablet should be wiped up with a damp disposable towel which must be thrown out. For the storage of unused broken tablets, see section 5 “How to store Siklos”.

Treatment follow-up

Your doctor will tell you how long to take Siklos.

When taking Siklos you will have regular blood tests and check your liver and kidney. Depending on the dose you take, these tests may be performed monthly or every two months.

Depending on these results your doctor will adjust your dose of Siklos.

If you take more Siklos than you should

If you take more Siklos than you should or if a child has taken any, contact your doctor or the nearest hospital immediately as you may need urgent medical treatment. The most common symptoms of overdose with Siklos 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 Siklos

Do not take a double dose to make up for a forgotten tablet. Continue as normal when it is time to take the next dose as prescribed by your doctor.

If you stop taking Siklos

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

4. Possible side effects

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

Tell your doctor immediately if you notice any of the following serious side effects:
- A severe infection,
- Tiredness and/or looking pale,
- Unexplained bruising (accumulation of blood under the skin) or bleeding,
- Unusual headache,
- Difficulties in breathing.

Tell your doctor as soon as possible if you notice any of the following side effects:
- Fever or chills,
- Feeling sick, or a general feeling of being unwell,
- Rash (itching red eruption of the skin),
- Ulcers or wounds on your legs,
- Sore (open skin infection) on your skin,
- Disorientation (confusion) and dizziness.

DETAILS OF SIDE EFFECTS

Very common side effects (may affect more than 1 in 10 people):
Low blood cell counts (myelosuppression), enlargement of red blood cells,
Absence or low amount of sperm in the semen (azoospermia or oligospermia). Siklos may hence decrease the ability of men to father children.

Common side effects (may affect up to 1 in 10 people):
Reduced number of red blood cells (anaemia), low platelet count, headache, skin reactions, inflammation or ulceration of the mouth (oral mucositis).

Uncommon side effects (may affect up to 1 in 100 people):
Dizziness, nausea, itching red eruption of the skin (rash), black nails (melanonychia), and hair loss.

Rare side effects (may affect up to 1 in 1 000 people):
Wounds on the legs (leg ulcers), and modification of liver function.

Very rare side effects (may affect up to 1 in 10 000 people) or unknown frequency (frequency cannot be estimated from the available data):
Inflammation of the skin causing red scaly patches and possibly occurring together with pain in the joints.

Isolated cases of malignant disease of blood cells (leukaemia), skin cancer in elderly patients, bleeding, gastrointestinal disturbances, vomiting, skin dryness, fever, absence of menstrual cycles (amenorrhoea), eye disease causing redness and pain of the eyes, sensitivity to light, and/or reduced vision (limbal stem cell deficiency). See also section 2. and weight gain.

Reporting of side effects
If you get any side effects, talk to your doctor or, 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 Siklos

Keep this medicine out of the sight and reach of children.

Do not use Siklos after the expiry date which is stated on the carton and the bottle after EXP.

Store below 30°C.

Unused broken tablets must be replaced in the bottle and must be used within three months.

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 to protect the environment.

6. Contents of the pack and other information

What Siklos contains

- The active substance is hydroxycarbamide.
  Each Siklos 100 mg film-coated tablet contains 100 mg hydroxycarbamide.
  Each Siklos 1 000 mg film-coated tablet contains 1 000 mg hydroxycarbamide.

- The other ingredients are sodium stearyl fumarate, silicified microcrystalline cellulose and basic butylated methacrylate copolymer.

What Siklos looks like and contents of the pack

Siklos 100 mg film-coated tablets are off-white, oblong-shaped tablets with a break line on both sides. The tablet can be divided into two equal parts.
Each half of tablet is embossed “H” on one side.
Siklos 100 mg is supplied in plastic bottles containing 60, 90 or 120 tablets.

Siklos 1 000 mg film-coated tablets are off-white, capsule-shaped tablets marked with three score lines on both sides. The tablet can be divided into four equal parts.
Each quarter of tablet is embossed “T” on one side.
Siklos 1 000 mg is supplied in plastic bottles containing 30 tablets.

All pack sizes may not be marketed.

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92200 Neuilly-sur-Seine
France

Manufacturer
Delpharm Lille
Parc d’Activités Roubaix-Est
22 rue de Toufflers
CS 50070
59452 Lys-lez-Lannoy
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.