SCIENTIFIC DISCUSSION

Introduction

Sickle Cell Syndrome (SCS) is one of the most commonly inherited diseases world wide, with an estimated prevalence in the European Union of 0.56 in 10,000 persons. Furthermore, the sickle β-globin gene is widely spread throughout Africa, the Middle East, Mediterranean countries and India and the frequency of sickle cell carriers is up to one in four in West Africans and 1 in 10 in Afro Caribbean's. It has reached such high levels in these latter populations because the silent carrier state protects against malaria.

SCS describes a group of inherited genetic conditions characterised by an abnormality (called variant S) of haemoglobin A (HbA). This family of haemoglobin disorders results from inheriting the sickle β-globin gene (S), which gives rise to abnormal haemoglobin, HbS. The sickle β-globin chain is the consequence of a single amino acid substitution in the chain (β-6 glutamic acid to valine), and sickle-cell syndrome is caused by combinations of two variant alleles of the β-globin gene, at least one of which carries the β-6 glu-val mutation. The most common and severe form of SCS is sickle cell anaemia, the homozygote (SS) situation where the sickle β-globin gene has been inherited from both parents. Other compound heterozygote conditions can also occur, featuring the same clinical problems as SCA, and these include combinations of a sickle β-globin allele with other structural variants of the β-chain (e.g. SC disease or with a β-thalassemia mutation giving rise either to Sβ0 or Sβ+). The presence of HbS causes SCS as this haemoglobin forms insoluble and viscous polymers under deoxygenated conditions, distorting the red blood cells (RBC) into the classis sickle shape. The intrinsic oxygen binding ability of HbS, however, is unaltered. The polymerisation of deoxygenated HbS is the primary event in the molecular pathogenesis of SCS, resulting in a distortion of the shape and increased rigidity of the RBC. The polymerisation of HbS upon deoxygenation also results in cellular dehydration and decreased deformability and stickiness of red blood cells that promotes their adhesion to vascular endothelium. These rigid cells are responsible for the chronic haemolytic anaemia and the vaso-occlusive phenomena that characterise the disease, and which can give rise to chronic organ damage.

The most common clinical problem is a painful vaso-occlusive crisis, which causes over 90% of acute hospital admissions, and significant morbidity in the community. While the problems are generally the result of small vessel vaso-occlusion, large vessel disease also occurs resulting in thrombotic cerebral vascular accidents, the acute chest syndromes (ACS) and/or placental infarction. ACS is an important complication as it is the second most common cause of hospitalisation in sickle cell patients and accounts for more than 25% of premature deaths in sickle cell disease. Death may also be caused by chronic organ failure or as a result of other acute catastrophic event such as a stroke, splenic sequestration or other complications. Recent *in vivo* studies in transgenic mice further suggest that vascular occlusion results in the creation of an inflammatory state that contributes to pathological sequelae. People with sickle cell disease are susceptible to a broad array of health problems, including anaemia, pain and serious infections. One of the major goals for therapy of SCS is to decrease the effective intracellular concentration of HbS and so reduce polymerisation in conditions of lowered oxygen tension with the intent of ultimately ameliorating vaso-occlusion, sickle cell painful crises and acute and chronic organ damage. The management of SCS is primarily palliative in nature, including supportive, symptomatic and preventative approaches to therapy. The methods of primary molecular and cellular therapy in patients with SCS include the induction of foetal haemoglobin (HbF), cellular rehydration, anti-adhesion therapy, NO and it's precursors, transplantation (curative treatment may involve allogeneic bone marrow transplantation) and gene therapy (although this is currently limited to investigational laboratory procedures). In terms of preventive treatment however, the use of agents that increase the production of HbF has been by far the most promising approach. The expression of globin genes is regulated during ontogeny, and in humans globin production is characterized by two major "switches"; production of embryonic haemoglobin switches after the first two months of gestation into the production of HbF and then again before birth into adult haemoglobin (HbA and HbA2). An increase in HbF in SCS ameliorates the clinical symptoms of the underlying disease as HbF-containing RBC (F cells) have both lower concentrations of HbS, and HbF directly inhibits

©EMEA 2007

polymerization of HbS, accounting for the lower propensity of such cells to form intracellular polymer and cause pathophysiologic consequences.

The beneficial effects of high levels of HbF in SCS have been recognized for many years following clinical and epidemiological observations, as well as laboratory studies. As early as 1948, it was noted that newborns with SCS do not manifest significant clinical problems related to their disease in the first 6 months of life until the HbF declines to adult levels. The level of HbF in normal adults is 1% or less with the HbF primarily sequestered in 1 to 5% of total circulating red cells. The number of these F cells and the overall level of HbF in circulating F cells are to a large degree determined by heritable traits, although levels of HbF can also be affected by environmental factors (e.g., erythropoietic stress, exposure to certain cytotoxin compounds). It has been shown that most patients with SCS from certain regions of Saudi Arabia and India who inherit a genetic determinant for high HbF (more than 50 mutations have been described that increase HbF synthesis in postnatal life) have a very mild sickling disorder, while a more recent large multicentre study of the natural history of SCS demonstrated an inverse correlation between HbF levels and the frequency of painful crisis and early death. Based on this evidence, therapeutic agents that increase HbF production have been developed for patients with this disorder.

About the product

Hydroxyurea (HU) or hydroxycarbamide (international non-proprietary name) is an antineoplastic drug that has been marketed over the world for several decades including in the US, Canada and the EU. HU is used in the treatment of melanoma, resistant chronic myeloid leukemia, recurrent metastatic or inoperable carcinoma of the ovary, epidermoid carcinomas of the head and neck, cervical cancer, haematological disorders and HIV. Its mechanism of action is believed to be based on its inhibition of the enzyme ribonucleotide reductase.

On July 9, 2003, the European Commission granted Orphan Medicinal Product Designation to Siklos (OTL Pharma) containing the active substance hydroxycarbamide (hydroxyurea, HU) for the treatment of Sickle Cell Syndrome (SCS).

– Indication

Siklos is indicated for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in paediatric and adult patients suffering from symptomatic Sickle Cell Syndrome. (see section SPC 5.1)

Treatment with Siklos should be initiated by a physician experienced in the management of Sickle Cell Syndrome.

– Posology

In adults, adolescents and children older than 2 years:

The posology should be based on the patient's body weight. 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. Under exceptional circumstances a maximum dose of 35 mg/kg b.w./day might be justified under close haematological monitoring (see section 4.4). The dosage of Siklos can be adjusted to body weight by increments of 250 mg by using a quarter of tablet. As long as the patient responds to therapy either clinically or haematologically (e.g. increase of haemoglobin F (HbF), Mean Corpuscular Volume (MCV), neutrophil count) the dose of Siklos should be maintained. In case of non-response (re-occurrence of crises or no decrease in crisis rate) the daily dose may be increased by 250 mg steps. In the event a patient does still not respond when treated with the maximum dose of hydroxycarbamide (35 mg/kg b.w./day) 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. Haematologic recovery usually occurs within two weeks. Treatment may then be reinstituted 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 < 2000 /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

©EMEA 2007

Sickle Cell Syndrome are available in children and adolescents, with a follow-up of 12 years in 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 treating physician and should be based on the clinical and haematological status of the individual patient.

Children less than 2 years of age

Because of the rarity of data on treatment with hydroxycarbamide in children less than 2 years of age, dosage regimens have not been established and thus, in this population, the treatment with hydroxycarbamide is not recommended.

Children and adolescents (2-18 years old)

In children and adolescents with Sickle Cell Syndrome, systemic exposure to hydroxycarbamide is similar to adult patients. Hence, no dose-adjustments are necessary in younger patients.

Renal impairment:

As renal excretion is a main pathway of elimination, dosage reduction of Siklos should be considered in patients with renal impairment. In patients with a creatinine clearance ≤ 60 ml/min the initial Siklos dose should be decreased by 50%. Close monitoring of haematologic parameters is advised in these patients. Siklos should 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 dosage adjustments in patients with hepatic impairment. Close monitoring of haematological 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 with the individual dosage, the tablet or the halves or quarters of the tablet should be taken once daily, preferably in the morning before breakfast and, where necessary, with a glass of water or a very small amount of food.

Quality aspects

Introduction

Siklos is presented as film-coated tablets containing 1000 mg of hydroxycarbamide as active substance. The tablets have a triple scoring line on both sides, which allows dividing them into four equal parts of 250 mg each.
The other ingredients include sodium stearyl fumarate, micro-crystalline cellulose and colloidal anhydrous silica and basic butylated methacrylate copolymer.
The tablets are packed in PVC/PVDC/Aluminium blisters.

Active Substance

Hydroxycarbamide is white to almost white, crystalline powder. It is hygroscopic, freely soluble in water and practically insoluble in alcohol. No evidence of polymorphism has been demonstrated. In any case hydroxycarbamide being freely soluble in water, the physical characteristics of the active are not considered critical.
A certificate of Suitability to the Monograph of the European Pharmacopoeia (R0-CEP 2003-015-Rev 02), listing additional tests and limits for any other impurities and residual solvents, is available for the manufacturer of the active substance.
Batch analysis data provided for 3 production-scale batches confirm compliance with the PhEur monograph.
No stability data have been provided and the certificate of suitability does not include a retest period or shelf-life for hydroxycarbamide. As a consequence, the active substance will be tested immediately prior to manufacture of the finished product.

©EMEA 2007

Medicinal Product

- Pharmaceutical Development

The objective was to develop an oral formulation, which allows administration to both adults and children while taking into account the dosage range.

The poor compression properties of hydroxycarbamide (very poor cohesion properties, very bad capacity to transmit forces into the powder bed and hygroscopicity resulting in intense sticking during compression) have been compensated by a suitable choice of excipients. Silicified microcrystalline cellulose allows direct compression and sodium stearyl fumarate is used as a lubricant to decrease the level of friction, to improve the transmission of force into the powder bed and to decrease friability. The ratio of active substance/excipients in the formulation has been optimised based on development studies in order to improve the manufacturing process.
In order to protect skin and mouth membranes from direct contact with antineoplastic hydroxycarbamide (see clinical and non-clinical section), the tablets are film-coated with basic butylated methacrylate copolymer. A coating soluble in organic solvents has been selected due to the sensitivity of the active to moisture. Concerning the risk of contact when breaking the tablets, recommendations on how to handle the tablets have been added in the product information and, the applicant was requested to develop an additional pharmaceutical form after opinion (see Discussion on chemical, pharmaceutical and biological aspects).

Uniformity of mass of both halves and quarters of tablets in line with PhEur has been demonstrated.

All the excipients are of PhEur quality. Regarding the TSE risk, Siklos does not contain any ingredient of ruminant origin.

Satisfactory specifications have been set up for PVC/PE/PVDC/Aluminium blister.

The finished product batch used in clinical trial had the same qualitative and quantitative composition as the commercial formulation.

- Manufacture of the Product

The manufacturing process consists of the standard following operations: blending, direct compression and coating.
Satisfactory in-process controls have been defined. Hydroxycarbamide being an antineoplastic agent, the equipment is dedicated to this type of agent.
Because of some variations in resistance to crushing observed for the tablet cores during development and the possible impact on breakability, the initial compression force has been modified during development. Moreover in order to improve the breakability of the tablets, the punch used to manufacture the product has been modified in order to increase the depth of the scoring lines and the shape of the tablets extended.
Validation data on 3 pilot scale batches and on 1 production scale batch have been provided and confirm that the process is sufficiently robust in order to ensure batch to batch consistency.

- Product Specification

The finished product specification includes tests for appearance, identity (IR and HPLC), assay (HPLC), degradation products (HPLC), urea (TLC), residual solvents (GC), uniformity of dosage units (PhEur), subdivision of tablets (halves and quarters), resistance to crushing (PhEur), disintegration (PhEur), dissolution (PhEur), and microbial limits (PhEur).
Batch analysis data provided for the validation batches confirm satisfactory compliance and uniformity with the proposed specification

©EMEA 2007

- Stability of the Product

- Stability of tablets

Stability data have been presented for 2 pilot scale batches and on 2 production scale batches.
Under long-term conditions (25°C/40% RH - commercial packaging) and under accelerated conditions (40°C/75% RH - commercial packaging) respectively up to 26-months and 6-month data are available. Stability data have also been provided under intermediate conditions (30°C/65% RH - commercial packaging).
The parameters tested included appearance, assay (HPLC), degradation products (HPLC), resistance to crushing (PhEur), disintegration (PhEur), dissolution (PhEur), and microbial limits (PhEur).
The observed changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SPC.
The data provided support the proposed shelf life and storage conditions as defined in the SPC.

- Stability of broken tablets

Satisfactory stability data for the broken tablets have been provided and support the proposed storage conditions defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The active substance is well characterised and documented. The pharmaceutical form selected is adequate taking into account the properties and the stability of the drug substance. The excipients are commonly used for this kind of formulation and the packaging material is well documented. The manufacturing process enhances to obtain reproducible finished product batches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life.
At the time of the CHMP opinion, there were a number of unresolved quality issues having no impact on the risk-benefit balance of the product. Among those, the subdivision of film-coated tablets for an antineoplastic agent was considered not optimal, and the applicant was requested to develop an additional pharmaceutical form more suitable for children as well as a child-resistant packaging. Moreover, recommendations on how to handle the tablets and how to store the unused broken tablets are mentioned in the SPC (section 6.6 Special precautions for disposal and other handling) and in the package leaflet (section 3. How to take Siklos and section 5. How to store Siklos) of the package leaflet. The applicant committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

Non-clinical aspects

Introduction

HU is a cytostatic agent that has no specific demethylating activity and which promotes methylation in a non-specific way. The precise mechanism by which HU produces its cytotoxic and cytoreductive effects is not known. Various studies (Yarbro, 1992; Choy, 1998; McClarty, 1987) support the hypothesis that HU causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor without interfering with the synthesis of ribonucleic acid or of protein. Ribonucleotide reductase is the enzyme that catalyzes synthesis of deoxyribonucleoside diphophosphates (dNDPs) from ribonucleoside diphosphates (rNDPs). Ribonucleotide reductase reduces the hydroxyl at carbon 2 of the ribose sugar in the rNDP to hydrogen, forming a deoxyribose sugar and a corresponding dNDP. A free-radical mechanism is involved in the reaction.

Pharmacology

- Primary pharmacodynamics

Increase of foetal haemoglobin levels in Red Blood Cells

HU increases HbF levels, thereby altering the kinetics and thermodynamics of haemoglobin S polymerisation (Atweh, 2003).*In vitro*, HU raised γ-globin levels by acting on early adult human

©EMEA 2007

erythroid progenitors (Stoeckert, 1994) as well as by interacting directly with late erythroid precursors that are already engaged in haemoglobin production (Fibach, 1993). HU increased total intracellular haemoglobin (Erard, 1981) in the human K562 erythroleukemia cell line and preferentially increased $^{G}\gamma$-globin mRNA levels in these cells (Xu, 1998). Furthermore, in two-phase mixed cultures of peripheral-blood mononuclear and erythroid progenitor cells from normal donors, HU significantly increased both γ-globin mRNA levels and HbF, and also had a comparatively small stimulatory effect on ß-globin mRNA expression (Smith, 2000). HU altered globin gene expression independently of its cytotoxic effects in erythroid progenitors derived from umbilical cord samples or peripheral blood from patients with HbS-hereditary persistence of HbF or homozygote sickle cell anaemia HU treatment led to the recruitment of a pool of non-proliferating HbF-programmed erythroid progenitors (Baliga, 2000).

HU administration augmented HbF production and inhibit *in vitro* growth of erythroid colonies from the blood of juvenile cynomolgus monkeys (Letvin, 1985). *In vivo,* HU (100 mg/kg b.w./d for 5 d) produced a "dramatic" increase in F cells and foetal haemoglobin in anaemic juvenile cynomolgus monkeys (Letvin, 1984).The effect of treatment with a combination of erythropoietin, stem cell factor and HU on HbF levels has also been evaluated in a baboon model (Lavelle, 2001).

Increased synthesis of Nitric Oxide

HU can be oxidized by haeme groups to produce the free-radical gas molecule NO (nitric oxide) *in vitro* (Stolze, 1990; Pacelli, 1996). Nitric oxide detected as nitrosyl haemoglobin or nitrosyl haemoprotein complexes is the result of the metabolism of HU (Jiang, 1997), generated in the presence and absence of catalase (Sakano, 2001). Chemical oxidation of HU produces nitric oxide and nitroxyl, the one-electron reduced form of NO. These oxidative pathways generally proceed through the nitroxide radical or C-nitrosoformamide. Biological oxidants, including both iron and copper-containing enzymes and proteins, also convert HU to NO or its decomposition products *in vitro* and these reactions also occur through these intermediates. A number of other reactions of HU, including the reaction with ribonucleotide reductase and irradiation, also demonstrate the potential to release NO (King, 2003). It is important to note that HbF induction by HU is mediated by the NO-dependent activation of soluble guanylyl cyclase. - Individual variations in NO signal amplification secondary to NO scavenging or sGC/phosphodiesterase activitiesexplain the variable responsiveness to HU treatment (Cokic, 2003).

Reduction in red cell – endothelial adhesion

In vitro, HU significantly and dose-dependently changes the morphology and monovalent cations composition of cultured vascular endothelial cells (Adragna, 1994). HU reduces adhesion molecule expression on sickle erythrocytes, including VLA-4 and CD36 which are found in unusually high numbers on sickle cell reticulocytes and mediate adhesion of sickle RBC to endothelium (Styles, 1997). HU reversibly, dose-dependently and significantly decreases the release of the vasoconstrictor peptide endothelin-1 (ET-1) through downregulation of ET-1 gene expression (SCS patients exhibit elevated serum levels of ET-1 during episodes of vaso-occlusive crisis and levels correlate with disease severity). In addition, HU reduces the expression of vascular cell adhesion molecule (VCAM-1) on endothelial cells. The mechanism by which HU reduces reticulocyte-endothelium adhesion is further explained (Brun, 2003).

Effects on sickle red cell rheology

Erythrocyte hydration status and deformability can be increased by HU (Adragna, 1994; Brugnara, 2001; Ballas, 2002; Davies, 2003). Cell dehydration induced by hypoxia is blunted by HU, suggesting a major role for the Gardos channel in hypoxia-induced dehydration *in vivo* (De Franceschi, 1999). HU can raise mean corpuscular volume and lower mean corpuscular Hb concentration without influencing HbF synthesis (Orringer, 1991).

Other effects

The inhibition of ribonucleoside diphosphate reductase by HU has also been studied in myeloproliferative disorders such as chronic myelogenous leukaemia and polycythaemia rubra vera. HU has also been investigated in the treatment of various solid tumours such as malignant melanoma, refractory ovarian cancer, squamous cell carcinoma of the head and neck, renal cell carcinoma, transition cell carcinoma of the urinary bladder and advanced prostate cancer.

©EMEA 2007

- Secondary pharmacodynamics

No secondary pharmacodynamics studies have been conducted.

- Safety pharmacology programme

No pharmacology studies addressing the effects on heart rate, body temperature, respiratory function or locomotive activity that are relevant to the present submission have been conducted.

- Pharmacodynamic drug interactions

One pharmacodynamic drug interaction study has been published, which investigated the combination of a single dose of vinblastine (an M phase cytotoxic agent) and a 5-day production course of HU (Letvin,1985).

Pharmacokinetics

- Method

An analytical HPLC method for determination of the assay and impurities has been conducted for the present submission. Recently published methods are also based on high performance liquid chromatography with electrochemical, ultraviolet or colorimetric detection (Pujari, 1997; Iyamu, 1998; Mannouilov, 1998) and are reported to be suitable for pharmacokinetic investigations (Pujari, 1997).

- Absorption

In vivo mouse studies have been published, showing that HU is 50% bioavailable after i.p. and p.o. administration of 300 mg/kg b.w. (Tracewell, 1994). The dose-concentration of i.p. HU in BALB/c *nu/nu* nude mice is linear at doses of between 50 and 200 mg/kg b.w. (Van den Berg, 1994). Complete absorption of the drug has been assayed from by the excretion pattern of orally and i.p. administered ^{14}C-HU in mice, with only 0.1% of the drug being excreted via faeces (Adamson, 1965).

- Distribution

HU enters cells via passive diffusion, and rapidly equilibrates in tissue and in blood. (Gwilt, 1998). The fate of HU has been evaluated in mice and rats following parenteral and oral doses (Adamson, 1965; Philips, 1967). HU is found at very low concentrations in the liver, at medium concentrations in lung and brain tissue, and highest concentrations in the kidney, during i.p.administration. HU rapidly diffuses into brain tissue, behaving in a dose-dependent manner up to 200 mg/kg b.w. A linear relationship between dose and concentration is observed at doses of 50 – 200 mg/kg b.w (Van den Berg, 1994). Distribution of HU into solid mammary model tumour tissue is rapid at a dose of 0.25 mg/g b.w. with HU concentrations being similar in blood and tumour tissue (Fabricius, 1971). HU distributes into human CSF and is transported from the CSF to sub-ependymal brain sites. HU is removed from the brain by probenecid- and digoxin-sensitive transport mechanisms at the blood-brain barrier. However, HU distribution to the CSF, choroid plexus and pituitary gland remains unaffected by other drugs. An organic anion transporter and p-glycoprotein are potentially implicated in the brain distribution of HU (Dogruel, 2003). HU is rapidly and widely distributed into breast milk, across the placenta and through the blood-brain barrier. This is consistent with the large volume of distribution in humans. Data on the extent of protein binding of HU have not been provided.

- Metabolism

After i.p. administration of ^{14}C-HU to mice, equal amounts of ^{14}C-HU and ^{14}C-urea totalling in aggregate over 80% of the dose can be found in urine 24 h after administration. ^{14}C-carbonate in urine and carbon dioxide in the expired air account for a further 11% of the ^{14}C. *In vitro* experiments indicate highest degradative activities for the formation of urea in kidney and liver (Adamson, 1965). HU is enzymatically reduced by liver tissue with the greatest amount of activity in hepatic mitochondria (Colvin, 1970). Furthermore, HU is a substrate for the enzyme urease *in vitro*. The rate of degradation of urea by urease is about 1,000 times that of HU, however, the degradation products of HU have not been identified and the contribution of urease to the metabolism of HU *in vivo* remains unclear (Davidson, 1963). HU forms methaemoglobin from oxyhaemoglobin with concomitant formation of the aminocarboxylaminooxyl radical H_2N-CO-HNO° and the production of NO (Stolze,

©EMEA 2007

1990; Pacelli, 1996). The *in vivo* production of NO is proven 3 h following the i.g. administration of HU (80 – 1,020 mg/kg b.w.) to rats (Jiang, 1997).

- Excretion

Following the i.p. administration of ^{14}C labelled HU (500 mg/kg b.w.) to mice, urinary excretion of over 80% of radioactivity in 24 h is observed. Respiratory $^{14}CO_2$ accounts for 7% and only very small amounts (<0.5%) appeared in the faeces (Adamson, 1965). In rats, the excretion pattern following i.p. administration of HU is similar to that of mice (Adamson, 1965).The portion of HU recovered in urine increases according to dose; i.e., from 30% after administration of 46 mg/kg b.w. to 70% after administration of 1,840 mg/kg b.w., respectively. The metabolic process could be operating at a maximal rate when tissue concentrations are high enough to saturate the enzyme system. In this case, renal excretion could be the dominant factor in the loss of HU. At lower concentrations metabolism could contribute more significantly to the excretion rate of HU (Philips, 1967). The elimination of HU has also been described by two pathways, one linear corresponding to renal excretion and the other nonlinear and consistent with Michaelis-Menten kinetics corresponding to metabolism (Tracewell, 1994). Small amounts of HU are also secreted into breast milk with therapeutic dosing. At 1h after treatment with 100 mg/kg b.w., the concentrations in the embryos exceed the maternal plasma concentrations. The elimination half-lives in embryos are appreciably higher compared with maternal plasma half-life (Wilson, 1975).

- Pharmacokinetic Drug interactions

Brain uptake of [^{14}C]H is affected by drug interactions; it increases by 200 µM HU, 90 µM D4T, 350 µM probenecid, 25 µM digoxin but not by 120 µM HU, 16.5 – 50 µM D4T, 90 µM 2'3'-dideoxyinosine or 90 µM abacavir. [^{14}C]HU distribution to the CSF, choroid plexus and pituitary gland remains unaffected by these drugs (Dogruel, 2003).

Toxicology

- Single dose toxicity

No detailed single-dose study reports have been submitted for this marketing authorisation application. Available information in the public domain and the literature mainly using another product containing HU approved in the U.S.A. (Hydrea, Bristol Myers Squibb) have been reviewed. In single-dose studies, mice and rats were exposed to single oral dose of HU and followed for a 14-day observation period. The acute median lethal dose was within 5,000 to 15,000 mg/kg b.w. depending on animal species and route of administration. Deaths were observed after several days. The major clinical sign observed was aplasia. The oral LD_{50} of HU is 7,330 mg/kg b.w. in mice and 5,780 mg/kg b.w. in rats.

Additionally, in male rabbits receiving a single i.v. injection of 150 mg/kg b.w. HU solution, there was an early but transient significant decrease in blood erythrocyte count (approximately 30% lower at day 3 after HU) with a gradual increase in their osmotic resistance, a suppression of granulocyte phagocytic capacity (approximately 50% at day 3), and a rapid increase in the proportion of lymphocytes without detectable lysosomes (2-fold at 24 h). Also, serum acid phosphatase activity was elevated at day 7 after HU, which may reflect a manifestation of cell injury. Histological analysis of the liver of BALB/c mice analogously treated with HU, revealed a marked hepatotoxicity of HU, manifested as dilation of the intercell cord spaces and bile capillaries, the appearance of numerous balloon cells, cells with pyknotic nuclei, undetectable nucleoli and necrosis; particularly in the centres of hepatic lobules. To explain the observed toxicities, it was hypothesised HU-initiated free radical-mediated reactions (Malec, 1989).

- Repeat dose toxicity (with toxicokinetics)

No detailed study reports for repeat-dose toxicity were submitted. The applicant reviewed available published information.

Twenty-eight day studies conducted in rats and dogs exposed to repeated oral or i.v. doses of HU up to 400 mg/kg b.w./d. demonstrated a dose-related toxicity in both species. The treatment-associated changes were characterised by a medullar aplasia, lymphoid depletion and a decrease in spermatogenesis. In rats receiving the highest doses, the only macroscopic observations were a thymic hypoplasia and a significant increase of bronchopulmonary infections. The deaths of animals appeared to be related to infections (Hydrea BMS, 1997).

©EMEA 2007

In repeat-dose toxicity studies in the rat, the most consistent pathological findings were an apparent dose-related mild to moderate bone marrow hypoplasia as well as pulmonary congestion and mottling of the lungs. At the highest dosage levels (1,260 mg/kg b.w./d for 37 d then 2,520 mg/kg b.w./d for 40 d), testicular atrophy with absence of spermatogenesis occurred; in several animals, hepatic cell damage with fatty metamorphosis was noted.

In the dog, mild to marked bone marrow depression was a consistent finding except at the lower dosage levels. Additionally, at the higher dose levels (140 to 420 mg or 140 to 1,260 mg/kg b.w./week given 3 or 7 d weekly for 12 weeks), growth retardation, slightly increased blood glucose values, and haemosiderosis of the liver or spleen were found; reversible spermatogenic arrest was noted.

In the monkey, bone marrow depression, lymphoid atrophy of the spleen, and degenerative changes in the epithelium of the small and large intestines were found. At the higher, often lethal, doses (400 to 800 mg/kg b.w./d for 7 to 15 d), haemorrhage and congestion were found in the lungs, brain, and urinary tract.

In the above studies (i.e., 40 d rat study, 12 week dog study, and 7 – 15 d monkey study) cardiovascular effects (changes in heart rate, blood pressure, orthostatic hypotension, ECG changes) and haematological changes (slight haemolysis and slight methaemoglobinaemia) were observed in some species of laboratory animals (not specified) at doses exceeding clinical levels..

HU induced high lethality in hypophysectomised and adrenalectomised male Wistar rats, whilst ablation of other endocrine glands had no effect on the toxicity of HU. Doses of 300 – 800 mg/kg b.w./d HU for 5 d were well tolerated by intact rats. Following 300 and 800 mg/kg b.w./d HU, lethality over 5 d was 100% and 71.4%, respectively, in pituitary-ablated rats. In similarly treated adrenalectomised animals, lethalities were 63.3% and 72.7%, respectively (Navarra, 1990).

In repeat toxicity studies, effects on the circulatory system were observed.

- Genotoxicity

Hydroxyurea is considered a genotoxic agent, as established from genotoxic studies (Suter, 1990; Ziegler-Skylakakis, 1985; Sofuni, 1996; Wangenheim, 1988; Sherwood, 1988; Hart, 1983; Chlopkiewicz, 1982; Lee, 2003), an its likely mechanisms are due to an inhibitory effect on ribonucleotide reductase but possibly also due to the CYP-dependent formation of genotoxic metabolites, namely hydrogen peroxide.

- Carcinogenicity

Although conventional long-term studies to evaluate the carcinogenic potential of HU have not been conducted, HU is presumed a trans-species carcinogen as evidenced by a number of non-clinical studies (Chlopkiewicz, 1982; Muranyi-Kovacs, 1972; Weisburger, 1977). It is important to note that the World Health Organization International Agency for Research on Cancer (IARC) considers that HU is not classifiable as to its carcinogenicity to humans due to the inadequate experimental evidence. Therefore, a carcinogenic risk under the treatment with HU cannot be excluded.

- Reproduction Toxicity

HU adversely affects reproductive performance in rats, as evidenced by the following studies (Droxia, BMS; Evenson, 1992; Spencer, 2000, Chaube, 1966; Wilson, 1975, Aliverti, 1980; Iwama, 1983; DeSesso, 2000; Chahoud, 2002; Woo, 2003; Woo, 2004; Butcher, 1972; Adlard, 1975). HU causes testicular atrophy, reducing sperm production in male rats while high doses induce high incidence of resorptions in rats on Day 7-11 of gestation. In male mice, HU at 500mg/kg b.w. causes up to 50% loss of testicular weight by day 29. HU crosses the placental barrier and damages embryos in rats. Repeated oral administration of HU during the organogenetic period at dose levels ranging from 50-450 mg/kg b.w. leads to a dose-dependent embryo-lethal and teratogenic effect with an evident dose response relationship. Live foetuses at term generally show severe ocular and craniofacial anomalies; hydrocephalus, cardiovascular abnormalities, vertebral and costal defects. Rat embryos are teratogenically more sensitive to HU than monkey embryos.

- Toxicokinetic data

No toxicokinetic studies have been submitted for this marketing authorization.

©EMEA 2007

- Local tolerance

No local tolerance studies have been submitted for this marketing authorization.

- Other Toxicity Studies

No studies on antigenicity, immunotoxicity, dependence or metabolites have been submitted for this marketing authorization.

Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) has been calculated, and the PEC value is less than 0.01ug/l. Siklos is unlikely to represent a risk for the environment following its prescribed usage. No phase II environmental effect analysis has been submitted for this marketing authorization.

Discussion on the non-clinical aspects

The active substance of Siklos is hydroxycarbamide (HU), whose precise mechanism of action has not been fully elucidated. HU has been in clinical use for several decades, initially for treatment of myeloproliferative disorders and later to reduce the frequency of painful crises in adult patients with SCS. No new non-clinical pharmacodynamic studies have been carried out by the applicant to investigate the efficacy of Siklos, as the clinical utility of HU has already been demonstrated in clinical trials and clinical practice and sufficient information is available in the scientific literature. The available information in the public domain and the literature has mainly been produced using another product containing HU but is considered relevant for the current application. Additional non-clinical tests are not considered necessary.

Following oral administration, HU is readily absorbed and peak plasma levels are reached within 1-4h. With increasing dose, disproportionately greater mean peak plasma concentrations are observed. No data on protein binding of HU are available. HU distributes rapidly and the volume of distribution approximates total body water.

The metabolism of HU is poorly characterized. It is assumed that urea is the main metabolite of HU. Since the enzymes involved in the biotransformation process have not been defined, possible drug interactions based on metabolizing enzymes such as CYP isoenzymes, cannot be excluded. The elimination half-life of HU is species-specific (mice<rat<monkey)hinting at the species-specific differences in metabolism and/or excretion pattern.

No detailed study reports of non-clinical toxicology studies have been submitted. Concerning single-dose toxicity studies, clinical data on overdosing are available. Acute mucocutaneous toxicity has been reported in patients receiving hydroxycarbamide at dosages 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.

The repeated dose studies reviewed provide limited information about the chronic toxicity of the HU. 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. safety pharmacology studies evaluating the effect of HU on the circulatory system have not been performed. Additional non-clinical toxicology tests are not considered necessary.

It is important to note that HU is unequivocally genotoxic in a wide range of test systems. However, conventional long-term studies to evaluate the carcinogenic potential of hydroxycarbamide have not been performed. Intraperitoneal administration of 125-250 mg/kg HU (about 0.5-1 times the maximum recommended human oral daily dose on a mg/m2 basis) thrice weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to control. HU is presumed to be a human carcinogen. In patients receiving long-term HU for myeloproliferative disorders, secondary leukaemia has been reported. It is unknown whether this leukemogenic effect is secondary to HU or is associated with the patient's underlying disease. Skin cancer has also been reported in patients receiving long-term HU.

No non-clinical study to determine the effect on prenatal and postnatal development has been submitted. Very few clinical data are available on the human growth and development after in utero

©EMEA 2007

exposure and/or exposure during lactation. However, this information has been adequately refelected in the SPC and additional non-clinical studies are not required.

Local tolerance has not been studied non-clinically. Administering the broken tablets with a small amount of food could minimise the contact of HU with the mucous membrane of the mouth and the throat. According to the environmental risk assessment, it may be assumed that Siklos is unlikely to represent a risk for the environment following its prescribed use in patients.

Clinical aspects

Introduction

Published pharmacokinetic data on hydroxyurea/hydroxycarbamide (HU) has been evaluated in cancer patients. However, to fill the gap of published data on the pharmacokinetics of HU particularly in SCS patients, an additional pharmacokinetic study meeting recent quality standards, has provided valid data on key pharmacokinetic endpoints i.e. absorption, distribution and excretion of HU in children as well as in adults under pseudo-steady-state conditions. This study also includes a bioequivalence study between the HU breakable tablets (Siklos) and HU capsules (Hydrea) in adults and of HU breakable tablets in children and adolescents of both genders with SCS.

Pharmacokinetics

In support of this marketing application, the following pharmacokinetic study was conducted:

- 1 multiple-dose study in SCS patients (5.3.1.2 Siklos)

In total, the following studies with HU have been conducted- including 4 studies in patients with cancer, 2 studies in patients with HIV, and 2 studies in patients with SCS. The table below summarizes the results.

Table 1: Pharmacokinetic parameters after oral dosing with HU

Report No.	**6502**		**9807**	**0117**	**8001**	**8001**	**9608**	**9817**	**9202**	**5.3.1.2 Siklos®**	**5.3.1.2 Siklos®**
Patients (n)	Cancer (9)	Cancer (21)	Cancer (26)	Cancer (16)	Cancer (6)	Cancer (6)	HIV (9)	HIV (9)	SCD (32)	SCS (11)*	SCS (16)
Dose	20 mg/kg	80 mg/kg	2 g single	80 mg/ kg every 3 d	500 mg/m^2 every 4 h	800 mg/m^2 every 4 h	500 mg bid	500 mg bid (+ ddI)	10-35 mg/kg/ d	21.37 mg/kg/ d, 14 d	20.83 mg/kg/ d, 7 d
C_{max} (µmol/l)	272.1	1,684	793.75	723-1,830	540	800	135	203	250 at 2 h (25 mg)	389	388
C_{trough} (µmol/l)	-	-	NR	NR	220	410	8.5	31	NR	14.3	11.2
t_{max} (h)	1.8	1.4	1.22	3	0.5-2	0.5-2	0.92	1.44	NR	0.75	1.19
$t_{1/2}$ (h)	-	-	3.32	NR	~2-4.7		2.5	2.63	NR	7.49	6.27
AUC (µmol/l/h)	-	-	3,759	NR	NR	NR	540	906	1,216 µg*ml/ h	1,637	1,782
Renal (%)	-	-	36.24	NR	35.9	28.7	NR	NR	62	36.90	58.32
MTD	-	-	-	-	-	800 mg/m^2	-	-	21.3 mg/kg	-	-

* children and adolescents

- 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. Low trough HU concentrations were reported at values of 14.3 µmol in children and 11.18 µmol/l in adults. The total exposure up to 24 h post-dose is 124 mg*h/l in children

©EMEA 2007

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.

No data on the effect of food on the absorption of HU have been submitted.

The pharmacokinetic data were similar after intake of HU breakable tablets and HU capsules in adult patients with SCD.

- Distribution

No clinical studies have been submitted to evaluate the distribution of HU in SCS patients. Based on published reports, HU 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. The distribution of of HU in cerebrospinal fluid is presented in different studies with contradictory results.

- Metabolism

The biotransformation pathways as well as the metabolites are not fully characterised. Urea is one metabolite of hydroxycarbamide. Hydroxycarbamide at 30, 100 and 300µM 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

The applicant submitted a study report on renal excretion. 36.9% and 58.32% of the dose were detected in urine in children and in adults respectively.

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.

- Dose proportionality and time dependencies

No studies were submitted about dose proportionality and time dependencies.

- Special populations

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

Paediatric: 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 SPC section 4.2).

Renal impairment: As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of Siklos in patients with renal impairment. In an open single-dose study in adult patients with Sickle Cell Syndrome the influence of renal function on pharmacokinetics of

©EMEA 2007

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 SPC sections 4.2 and 4.4)

Close monitoring of haematological parameters is advised in these patients.

Hepatic impairment: There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment, but, due to safety considerations, Siklos is contraindicated in patients with severe hepatic impairment (see SPC section 4.2). Close monitoring of haematological parameters is advised in patients with hepatic impairment.

- Pharmacokinetic interaction studies

There are no data on the concomitant use of HU with other drugs in humans; there are also no prospective studies on the potential for HU to interact with other drugs. However, no case reports on interactions are present in the databases, indicating that there is no high potential for interactions.

- Pharmacokinetics using human biomaterials

No studies have been conducted to assess the pharmacokinetics of HU, using human biomaterials.

Pharmacodynamics

- Mechanism of action

HU belong to the pharmacotherapeutic group of "other antineoplastic agents", ATC code: L01XX05. The mechanism of action of HU in SCD is not definitely known.

- Primary pharmacology

Decrease of neutrophil counts

While the impact of HU in SCS was initially thought to be attributed to the rise in HbF, further study has revealed that while HbF appeared to play a significant role in early improvement in treated patients, the clinical response from three months of treatment was more significantly associated with a reduction in neutrophil count. Interestingly, after two years of treatment, half of the patients had no increase or only trivial increments in HbF despite significant amelioration of the disease in the treatment group (Davies, 2003). Although the reduction in neutrophils on treatment is a result of the cytotoxicity of HU, it is also suggested that the association of crisis rate with neutrophil count is a biological phenomenon. High neutrophil counts were associated with a worse clinical prognosis and earlier death. Therefore, neutropenic effects of HU may also be important in the reduction of symptoms. Neutrophils are known to adhere to vascular endothelium thus potentially impeding the flow of the sickle cells; neutrophils can also increase blood viscosity, release cytokines and are also involved in the inflammatory response. Finally, adherence of sickle cells to neutrophils followed by activation and production of toxic oxygen radicals has also been reported (Davies, 2003).

Increased synthesis of NO

Patients taking HU show a significant increase in iron nitrosyl haemoglobin and plasma nitrite and nitrate within 2 h of ingestion, providing evidence for the *in vivo* conversion of HU to NO. Formation of NO from HU may explain a portion of the observed effects of HU treatment (King, 2003). Although, at present, the mechanism (or mechanisms) of NO release, the identity of the *in vivo* oxidant and the site of metabolism remain to be identified, recent evidence suggests several lines of evidence for an involvement of NO. It has been shown that HU can be oxidized by haem groups to produce the free-radical gas molecule NO *in vivo* (Jiang, 1997; Glover, 1999). Advantages of NO production in SCS include a major role in maintaining vascular tone, a possible inhibitory role in HbS polymerisation, inhibition of platelet aggregation, as anti-adhesive therapy for ischaemia/perfusion injury and by improving endothelial function (Hong, 2002; Davies, 2003).

©EMEA 2007

Reduction in red cell – endothelial adhesion

In patients with homozygous sickle cell disease, within two weeks of commencing HU therapy and prior to any rise in HbF, sickle erythrocytes showed reduced adhesion to endothelial cells under low shear flow conditions. The lower adhesion of sickle RBCs to endothelium may facilitate escape from the microcirculation before polymerisation begins (Bridges, 1996).

Effects on sickle red cell rheology

Erythrocyte hydration status and deformability can be increased by HU (Adragna, 1994; Brugnara, 2001; Ballas, 2002; Davies, 2003). The effect of HU with respect to mean corpuscular volume was investigated in patients with sickle cell anaemia. The following pattern was seen in the sickle cell patients during HU treatment. Although the mean corpuscular volume of their RBCs increased, there was no change in mean corpuscular Hb concentration, ion content or mean density. A notable change in the sickle cell patients' blood was that two subpopulations of cells were almost eliminated during HU treatment; the hypodense reticulocyte fraction and the hyperdense fraction that contains irreversibly sickled cells. Therefore, the beneficial effect of HU might be due not only to an increase in HbF alone, but perhaps also to the associated increase in mean corpuscular volume or the altered RBC density profile (Orringer, 1991).

- **Secondary pharmacodynamics**

The inhibition of ribonucleoside diphosphate reductase has also enabled the use of HU in myeloproliferative disorders such as chronic myelogenous leukaemia and polycythaemia rubra vera. HU is anti-mitotic and cytotoxic depending on the concentration used, the duration of exposure, and the sensitivity of the organism. HU has also been investigated in the treatment of various solid tumours such as malignant melanoma, refractory ovarian cancer, squamous cell carcinoma of the head and neck, renal cell carcinoma, transition cell carcinoma of the urinary bladder and advanced prostate cancer. The use of HU at low concentrations has also been used to re-establish tumor sensitivity to chemotherapeutic agents or to decrease tumourigenicity (Timson, 1975; Gwilt, 1998; Hong, 2002). In addition, HU is also used to treat plaque psoriasis, usually at the dose of 500mg to 1g orally daily, in patients resistant to other therapies such as methotrexate, acitretin or phototherapy. In psoriasis, HU is though to work by reducing the replication of DNA within the basal cell of the epidermis. HU has known adverse effects such as temporarily lowering the number of white blood cells (increasing the chance of getting an infection) and lowering the number of platelets (impairing proper blood clotting). The major secondary pharmacodynamic effect observed with HU is haematological toxicity and results from a bone marrow suppression.

Discussion on clinical Pharmacology

- Pharmacokinetics

HU is well-established in SCS and is therapeutically used over a long time. Additional pharmacokinetic studies on these objectives are unlikely to produce information altering the clinical use of HU, since the side effects and the conditions of clinical use of HU are already well-known from long-term use in cancer as well as in SCS.

The pharmacokinetics have been adequately studied in the target population, i.e. in children. The mean age of children and adolescents was 10.25 years. The pharmacokinetic data were similar after intake of HU breakable tablets and HU capsules in adult patients with SCD.

The trough levels of HU were rather low in children when compared with adults. The once daily administration could be questioned based on $T_{1/2}$. The half-life doubled in patients treated by HU for SCD, when compared with that in patients treated by HU for other diseases. The Applicant should discuss the major difference.

There were no significant differences between pharmacokinetic parameters of HU in adults and in children. The Applicant has given no data on the influence of food on HU absorption.

A non-linear relationship between plasma HU concentrations and dose is apparent in nearly every animal and human pharmacokinetic study. The Applicant should discuss this special relationship, and also comment on the two following points. Is there a plasma concentration threshold to ensure a

©EMEA 2007

therapeutic efficacy? Recently, an author suggested that the marked differences in urinary HU concentrations could explain some of the differences in response to HU.

It has been demonstrated that the half-life of HU is longer is patients with renal impairment. In the SPC, HU is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min), while a dose reduction (by 50%) is recommended in patients with renal impairment (creatinine clearance < 60 ml/min). These recommendations are deemed sufficient to ensure the safety of HU in patients with renal impairment.

- Pharmacodynamics

HbF seems to be a good surrogate of HU efficacy in SCD. No severe adverse effects consecutive to vaccination with live vaccines have been reported in children with SCD, the patient should undergo the recommended vaccination programs including live vaccines.

As no data are provided on the interaction of HU with HIV drugs, the Applicant has committed itself to collect these data as part of the Risk Management Plan.

Clinical efficacy

- Dose response study(ies)

No dose response study has been submitted.

- Main study(ies)

Children

The applicant has submitted all clinical studies performed in children based on the published literature (see Tables 2 - 5). VOC was defined as any painful episode involving the extremities, abdomen, back, or chest, including acute chest syndrome.

Table 2 Summary of the clinical studies in children: biological parameters.

				Biological Parameters					
				Hb (g/dl)		WBC (10^9/l)		HbF (%)	
Author, year	Number (Age) means	Dose (mg/kg)	Follow-up (months)	Baseline	Change After HU	Baseline	Change After HU	Baseline	Change After HU
Braga, 2005 open-label	9 (13 years)	15-25	15	8.1 ± 0.8	8.0 ± 0.9	5.4 ± 2.5	4.4 ± 2.1	7.0 ± 3.9 %	13.7 ± 5.3 %
Ferster, 1996 simple-blind (PLACEBO)	22/22 (9 years)	20-25	6	8.1 ± 0.75	8.5 ± 0.83	12.47 ± 4.58	8.90 ± 2.51	4.65 ± 4.81	15.34 ± 11.3
Hankins, 2005 HUSOFT	21 (median:3.4 years)	20-30	4-6 years	8.5 ± 1.4	9.1 ± 1.4 (year 4) 9.0 ± 1.6 (year 6)	12.6 ± 4.4	10.1 ± 7.3 (year 4) 8.9 ± 4.2 (year 6)	21.8 ± 7.8	23.7 ± 7.4 (year 4) 23.3 ± 7.8 (year 6)
Jayabose, 1996 open-label	15 (median:15.3 years)	20-35	15-23	7.2 ± 1.7	8.5 ± 2.2	16.6 ± 5.0	11.5 ± 4.8	3.9 ± 2.5	17.8 ± 6.2
Kinney, 1999 HUG-KIDS STUDY	84 (9.8 years)	15-30	24	7.8 ± 1.0	9.0 ± 1.1	13.6 ± 3.9	9.2 ± 3.0	7.3 ± 4.9	15.5 ± 7.3
Koren, 1999 open-label	19 (15 years)	16-31	40.3 ± 13 (mean)	7.98	10.3 (36	19.0	10.8 (36	6.0	25.5 (36 months)

©EMEA 2007

			(20 to 68)		months)		months)		
Maier-Redelsperger, 1998 (pharmacodynamic)	29 (10.9 years)	20-40	36	8.4 ± 1.2	8.9 ± 1.1	7.2 ± 2.9	4.2 ± 2.6	6.1 (females) 3.5 (Males)	Great Variation from 3.3 to 36.2
Scott, 1996 open-label	13 (10-17 years)	10-35	24	8.2 ± 1.0	9.5 ± 1.5	not mentioned		6.9 ± 6.2	15.2 ± 9.8
Wang, 2001 open-label	28 (15 months median age)	20	24	8.5	8.8	12.7	10.1	21.9	22.6
Ware, 1999	16 (12.1 years)	15-30	22 (median value)	not mentioned	9.4 ± 1.3	not mentioned		not mentioned	20.6 ± 8.0 %
Zimmerman, 2004	122 (11.1 years median age)	20-35	7 years (average 4 years)	8.2 ± 1.2	9.7 ± 1.3	12.4 ± 3.8	7.0 ± 2.6	7.6 ± 5.5	19.1 ± 8.5

Table 3 Summary of the clinical studies in children: clinical parameters.

				Clinical Parameters					
	Number (Age)	**Dose**	**Follow-up**	**VOC pt/year (mean)**		**Hospital Admissions**		**Hospitalization pt/year DAYS**		**ACS Frequency**
Author, year	**means**	**(mg/kg)**	**(months)**	**PRE-HU**	**HU**	**PRE-HU**	**HU**	**PRE-HU**	**HU**	
Braga, 2005 open-label	9 (13 years)	15-25	15	0.5 ± 0.5	0.1 ± 0.2	1.3 ± 0.7	0.4 ± 0.6	11.9 ± 7.3	2.8 ± 5.2	number of ACS/ year decreased by 25 %
Ferster, 1996 simple-blind (PLACEBO)	22/22 (9 years)	20-25	6	↘ ↘		↘ with HU compared with placebo		↘ with HU compared with placebo		Low frequency 8 events / 254 patient - years
Hankins, 2005 HUSOFT	21 (median:3.4 years)	20-30	4-6 years	Not different From expected incidence		Not Evaluated		Not Evaluated		7.5 events / 100 person-years compared with 24.5 among historical controls
Jayabose, 1996 Open-label	15 (median:15.3 years)	20-35	15-23	2.5	0.87	not evaluated		not evaluated		Included in VOC analyses
Kinney, 1999 HUG-KIDS STUDY	84 (9.8 years)	15-30	24	76 events reported		not evaluated		not evaluated		10 events reported

©EMEA 2007

Koren, 1999 Open-label	19 (15 years)	16-31	40.3 ± 13 (mean) (20 to 68)	3	1	not evaluated	20 5.2	number of ACS / year decreased by 33%
Maier-Redelsperger, 1998 (pharmacodynamic)	29 (10.9 years)	20-40	36	not evaluated		not evaluated	not evaluated	not evaluated
Scott, 1996 Open-label	13 (10-17 years)	10-35	24	not evaluated		7 ± 2.4 (median) 3.0 ± 4.0 (median)	46.8 13.2	not evaluated
Wang, 2001 Open-label	28 (15 months median age)	20	24	not evaluated		not evaluated	not evaluated	not evaluated
Ware, 1999	16 (12.1 years)	15-30	22 (median value)	not mentioned	no VOC developed during therapy	not evaluated	not evaluated	No case of ACS
Zimmerman, 2004	122 (11.1 years median age)	20-35	7 years (average 4 years)	not evaluated		not evaluated	not evaluated	not evaluated

The Applicant has initiated an update of the two existing registries, the French patient registry and the Belgian paediatric cohort to provide data on the long-term efficacy and safety of HU. In the **Belgian cohort** 155 patient-years corresponded to a HU dose of 20 to 25 mg/kg/day and 42 patient-years corresponded to HU doses higher than 25 mg/kg/day. At one year, 85% (92/109) of patients had no major events requiring hospitalisation, while at 6 and 8 years 25% and 36% remained event-free, respectively. In the **French cohort** the comparison of a 7-day /week and a 4-day/week regime of HU revealed no difference with regards to tolerability, but failure rate was lower with the former regime (12/138 [8.7%] versus 14/45 [31%], p<0.001).

In the Belgian registry, 93 patients with SCD were followed (see table 8). Seven children were younger than 2 years at enrolment, 20 were between 2 and 5 years, 33 between 5 and 9 years, 27 between 10 and 19 years, and 6 were 20 years or older. The initial HU dose was 20 mg/kg/day and could be escalated by 5 mg/kg based on physician's judgment. At the end of the first year 55% of patients were treated with 20 to 25 mg/kg/day, 41% with < 20 mg/kg/day, and 4% with 25 to 30 mg/kg/day (n=1:>30).This distribution remained unchanged during the following years. During first, second, third, forth and fifth year of HU treatment 84%, 79%, 81%, 90% and 74% of patients were free of VOCs requiring hospitalisations. The number of hospitalisations significantly declined from the year prior to study to the end of the first year (p=0.0002), whereas no significant differences were observed in year-to-year comparisons from year 1 to 5.

Table 4 Clinical outcome in SCD patients before and during HU therapy in the Belgian registry.

	Before HU	**1 y HU**	**2 y HU**	**3 y HU**	**4 y HU**	**5 y HU**
Evaluable patients (n)	93*	82	61	44	33	22
Hospitalisations/year (n, mean ± SD)	2.76 ± 2.3	1.15 ± 1.9[c]	1.08 ± 1.5[c]	1.11 ± 1.5[c]	1.33 ± 2.1[d]	1.2 ± 1.5[b]

©EMEA 2007

Days in hospital (mean ± SD)	18.1 ± 17.3	7.3 ± 15.8[c]	5.4 ± 9[c]	4.9 ± 7.2[c]	9.1 ± 13.3[b]	9.4 ± 13[a]

* 78 patients of 93 patients registered are evaluable for hospitalisations in the year before entry in the registry.[a] NS, [b] p<0.05, [c] p<0.01, [d] <0.02 vs. baseline; paired t test

In parallel to the French paediatric registry, 43 of 202 children with SCD followed-up in a paediatric clinic in France were treated with HU since 1992 during at least 12 months. Compared to baseline a significant decrease of hospitalisation number (1.12 versus 2.85/year), hospitalisation days (6.43 d/year versus 19.45 d/year), VOCs (1.27/year versus 2.34/year) and ACSs (0.12/year versus 0.41/year, all p<0.001) was seen under HU. The responsible was variable with full success in 40% of patients, partial success in 21%, transitory success in 14%, and failure in 23%. **The initial HbF was the only factor predictive of response** (p=0.04). Haematological toxicity requiring withdrawal of HU was not observed.

In Israel, nineteen children and adolescents with a history of at least three acute painful events (severe VOC or ACS) per year were followed over a 2-year period. The children received HU with a mean of 21.3 mg/kg/day (16.4 to 31.2). A severe VOC was defined as an event requiring hospitalisation or a home crisis requiring analgesics for more than 24 hours. The mean follow-up was 40.2 months (20 to 66). HU considerably decreased all clinical endpoints. In patients with HbSS the VOC rate and the duration of hospital stay decreased more markedly than in points with compound heterozygous SCD (see table 9).

Table 5 Clinical effects of HU in children and adolescents in Israel

Parameter	Before HU (24 mo)			During HU (24 mo)			p-value
	Total	Incidence/year*	Event/pt-y	Total	Incidence/year*	Event/pt-y	
VOC (total)	123	61.5 ± 5.5	3	39	19.5 ± 6.5	1	<0.1
HbSS	66	33 ± 8	3.7	7	3.5 ± 1	0.4	=0.1
HbS/ß-thal	57	29 ± 3	2.9	32	16 ± 6	1.6	<0.1
ACS	22	11 ± 0		7	3.5 ± 1.5		<0.1
Haemolytic crisis	13	6.5 ± 0.5		1	0.5 ± 0.5		=0.05
Blood transfusion	208	104 ± 5	5.4	21	10.5 ± 6.5	0.55	<0.01
HbSS	100	50 ± 4	5.6	4	2 ± 2	0.22	<0.001
HbS/ß-thal	108	54 ± 1	5.4	17	8.5 ± 5	0.9	=0.02
Hospital days	764	382 ± 8	20	200	100 ± 1	5.2	=0.01

To summarise, in all clinical trials reduced SCD relevant outcomes were observed, such as VOCS, frequency of ACSs, hospital days, and also transfusion requirements. However, the efficacy of HU in stroke prevention has not been demonstrated.

Medium HU doses are effective in the majority of patients. This point is supported by the analysis of haematological response in the MSH study (Charache, 1996). The patients were stratified by HbF response (4 quartiles) and in the quartile with the highest HbF response 66% and 20% of patients received 15 to22.2 and 25 to 32.5 mg/kg/day HU, respectively (12% < 15, 3% 35 mg/kg/day). Among the patients with the lowest or no HbF response, 35% were treated with 35 mg/kg/day. In the Belgian cohort (426 patient-years) 229 patient-years corresponded to less than 20 mg/kg/day HU, 155 to 20 to 25 mg/kg/day, and 42 to HU doses above 25 mg/kg/day. A predominance of medium initial HU dose was also seen in the French cohort.

In several studies HU does were increased as long as pre-defined myelosuppression was absent up to a maximum dose.

In the MSH Study, statistical analysis revealed no change of the beneficial clinical effect of HU during two years of treatment. Clinical response began to emerge within two months and evident at 4 months. In the Belgian cohort the cumulative probability of not experiencing any event during at least 5 years of HU treatment was 47%. A sustained clinical benefit was demonstrated for HU in patients remaining

©EMEA 2007

on treatment for up to 8 years. In the French cohort, there was a secondary failure with recurrence of painful events after 6 to 82 months in 10 patients (7.5%).No reasons therefore were identified. However, especially in the French adult cohort non-compliance was a major problem.

In total, 378 children were followed in these studies during 6 months to 7 years. All studies were open label trials or extensions for long-term use of HU, but one study was a double-bind, placebo-controlled trial (**Ferster**, 1996). In this study, the change in HbF value was highly significant and correlated with the increase of MCV. In addition, in 16 patients, a complete disappearance of vaso-occlusive events requiring hospitalisation occurred within the first month of HU treatment. However, 6 patients experienced no relevant change in the number of crises requiring hospitalisation. In these 6 patients, the HbF level only slightly increased from 1.7% to 3.2%. The percentage of non-responders was thus 27%. Overall, the number of hospitalisations was reduced when patients were on HU therapy when compared with placebo. 16 of 22 patients did not require any hospitalisation for painful episodes when treated with HU as compared with only 3 of 22 when treated with placebo. The number of days in hospital was also significantly lower when patients were on HU therapy (range, 0 to 19 days) than when they were on placebo (range, 0 to 104 days).

In most other studies, there was a significant increase in HbF from baseline after use of HU. This increase was highly significant at 6 months. In the two extension studies (Hankins, 2005; Zimmerman, 2004) the mean percentage HbF values were sustained at approximately 20% even after 7 years of continuous HU therapy. The **threshold of HbF** for obtaining clinical efficacy could be comprised between 15 and 20%. Finally, the response on HbF levels could be improved by increase the HU dosage, from 20mg/kg/day till 35mg/kg/day. Only in one study (Maier-Redelsperger, 1998), the maximal dose of 40 mg/kg/day, as it is stated in the SPC, was reached.

The **haemoglobin level** also increased in all clinical studies and was sustained over the 7-year period.

In all studies where it was evaluated, the frequency of **VOC** decreased dramatically (by 66% to 80%), after the use of HU. The same dramatic response was observed for the number of **hospital admissions** and the number **days of hospitalisation**. Finally, the number of **ACS** (Acute Chest Syndrome)/year decreased by 25 to 33%. Considering that there are non-responders to the treatment, these improvements do demonstrate the overall efficacy of HU therapy. The remaining questions concern the actual link between HbF and efficacy (see the pharmacodynamics) and the ideal therapeutic dosage of HU.

The influence of the HU treatment on **stroke** has not been fully assessed by the Applicant. Ohene-Frempong (1998) emphasised the high incidence of cerebrovascular accident (CVA) in SCD patients. The highest rates of prevalence of CVA (4.01%) and incidence (0.61 per 100 patient-years) were in sickle cell anaemia (SS) patients, but CVA occurred in all common genotypes. The MSH study (Charache, 1995) did not show a statistical reduction in stroke. Halsey (2003) considered that there is no evidence that HU can reduce the incidence of first or recurrent strokes. Ware et al (1999) discontinued transfusions and gave HU to 16 paediatric patients with SCD and stroke. HU was started at 15 mg/kg/day and escalated to 30 mg/kg/day based on haematological toxicity. The results suggest that HU may be effective in the clinical setting of CVA disease in patients with SCD. The mechanisms by which HU might provide protection against stroke recurrence are not known, but the increase in HbF levels is likely to be important in the prevention of in vivo sickling within the stenotic cerebral vessels. In this study, the patients achieved an average %HbF of approximately 20%.

Platt (1994) followed 3,764 patients who ranged from birth to 66 years of age and investigated the circumstances of death for all 209 patients who died during the study. The median age of death was 60 years for males and 68 years for females. Among adults with SCD, 18% of the deaths occurred in patients with overt organ failure, predominantly renal. 33% were clinically free or organ failure but died during an acute sickle crisis (78% had pain, the chest syndrome, or both; 22% had stroke). Thus the acute chest syndrome, renal failure, seizures, a baseline white-cell count above 15,000 cells/mm^3 , and a low level of foetal haemoglobin were associated with an increased risk of early death. In the Cooperative Study of Sickle Cell Disease (Gill, **CSSCD**, 1995), 694 infants with confirmed SCD were enrolled at less than 6 months of age. The nature and the frequency of complications were followed prospectively over a 10-year period. Painful crises and acute chest syndrome were the most common sickle cell-related events. The mortality rate was low in this cohort: 20 children, all with HbSS, died. Infection, most commonly with Streptococcus pneumoniae and Haemophilus influenzae, caused 11

©EMEA 2007

deaths. Two children died of splenic sequestration, 1 of cerebrovascular accident, and 6 of unclear causes. The mortality rate was highest between 6 months and 3 years of age. On the other hand, a WBC > 15 x 10^9 is associated with an increased risk of early death in SCD (Charache, 1996).

Acute chest syndrome is a significant cause of morbidity and mortality in SCD. Solis et al (2005) performed a retrospective review of all the episodes of ACS diagnosed in their center in patients younger than 18 years with SCD. 23 episodes of ACS were evaluated in 8 out of 12 patients with SCD. The most frequent cause was infection. The most frequent symptoms were fever (87%), cough (61%) and cold (35%) symptoms. Children aged more than 3 years old had more severe episodes, with greater clinical compromise and radiological involvement and increased use of analgesia.

Steinberg et al (2003) conducted a study to determine whether HU attenuates **mortality** in patients with SCD (patients from the MSH study). 299 adult patients with frequent painful episodes enrolled in the follow-up. Patients were randomly assigned to receive HU (n=152) or placebo (n=147). 75 of the patients died, 28% from pulmonary disease. Patients with reticulocyte counts less than 250,000/mm^3 and haemoglobin levels lower than 9 g/dl had increased mortality. Individuals who had acute chest syndrome during the trial had 32% mortality compared with 18% of individuals without acute chest syndrome. Patients with 3 or more painful episodes per year during the trial had 27% mortality compared with 17% of patients with less frequent episodes. Taking HU was associated with a **40% reduction in mortality** (p=0.04). Cumulative mortality at 9 years was 28% when HbF levels were lower than 0.5 g/dl after the trial was completed compared with 15% when HbF levels were 0.5 g/dl or higher (p=0.03). These findings occurred in adults; how HU affects mortality in young children is unknown. Nevertheless, these observations confirm the link of HbF to mortality in SCD and suggest that the ability of HU to increase levels of HbF may be associated with reduced mortality. The authors found no relationship between decrements in neutrophil counts and mortality, but the Cooperative Study of Sickle Cell Disease (CSSCD, Gill, 1995) found that lower leukocyte counts were associated with longevity.

In two cases, chronic HU therapy has reversed **splenic dysfunction** (Claster, 1996). Splenic infarction is of great concern to providers who car for young children with SCD. The exact mechanism of the HU-induced effect on the spleen is unclear. The reversal of splenic dysfunction induced by HU in two young adults suggests a clearly positive expected effect when HU is administered to children. Early HU therapy might prevent functional hyposplenism in this group of patients. Wang et al (2001) reported a lower frequency of functional asplenia (47%) in children compared with the expected frequency from historical data of 80% as assessed by radionucleotide scanning. This fact was confirmed by the extension study HUSOFT (Hankins, 2005), suggesting that HU therapy can prevent loss of spleen function or even restore it.

Quality of life data are mentioned in the MSH study (Charache, 1995). These are presented as changes in baseline of three measures from the "Health Status Survey" (nine scales), the "Profile of Mood States" (four scales) and the "Ladder of Life". At 12 months general health perception was 1.6 above baseline in the treated group and 1.0 in the placebo group. A later report from the MSH study reported marginal but not significant improvement in general health perception at the end of the study (Cochrane, 2005).

Adults

The applicant has submitted all clinical studies performed in adults based on the published literature.

MSH study, a double-blind randomized study, has enrolled SCD adult patients with severe disease (at least 3 painful crises per year). It has assigned hydroxycarbamide to 152 patients and placebo to 147 controls. Patients given hydroxycarbamide received an initial dose of 15 mg/kg/day, which was increased by 5 mg /kg/d every 12 weeks unless marrow depression occurred (indicated by neutrophil count < 2.0 x 109/L, reticulocyte or platelet count <80 x 109/L, or Hb level <4.5 g/dl,). In the case of marrow depression, treatment was stopped until the blood count recovered and was then resumed at a dose 2.5 mg/kg lower than that associated with marrow depression. This defined the maximum tolerated dose (MTD). The hydroxycarbamide-treated patients had a lower annual rate of crises than the controls (2.5 vs 4.5 crises per year, p<0.001), fewer patients had chest syndrome (25 events vs 51, p <0.001), and fewer underwent transfusions (48 vs 73, p = 0.001). The study was early discontinued because of the benefits observed in the treated patients.

©EMEA 2007

430 adult patients were enrolled in several clinical studies, confirming these findings.

The Applicant has also initiated a retrospective, uncontrolled, multicentric follow up registry in 2 hospitals in France. The objective of this retrospective open follow up in adults diagnosed with homozygous sickle cell syndrome and treated off-label with hydroxycarbamide was to collect data on the long term safety and efficacy of this treatment and provide updates which would complete information already reported in the literature. The data of 123 adult SS patients have been collected. The hydroxycarbamide treatment was maintained in 76% of patients, with 41 patients (33%) treated for more than 5 years and 11 of them (9%) treated with HU for more than 10 years, with no serious toxicity related to HU. Mean dose (±SD) of HU was 16.4 ± 5.8 mg/kg/day at the beginning of the treatment and 18.5 ± 6.3 mg/kg/day at the end of the follow-up, with approximately two-thirds of patients receiving a daily HU dosage in the 15 to 25 mg/kg range. in terms of number of VOC with hospitalisation and HbF rate growth, the results were supportive of the efficacy in adult patients described in the literature.

- Clinical studies in special populations

See Main studies.

- Supportive study(ies)

See Main studies

Discussion on clinical efficacy

No detailed clinical study report on clinical efficacy have been submitted. HU has been in clinical use for several decades, initially for treatment of myeloproliferative disorders and later to reduce the frequency of painful crises in adult patients with SCS. No additional clinical efficacy studies are considered necessary. The applicant has presented bibliographic data for a total of 378 children who were followed in these studies during 6 months to 7 years.

In most clinical studies, there was a significant increase in HbF from baseline after HU use. This increase was highly significant at 6 months. In the two extension studies (Hankins, 2005; Zimmerman, 2004) the mean percentage HbF values were sustained at approximately 20% even after 7 years of continuous HU therapy. The threshold of HbF for obtaining clinical efficacy could be comprised between 15 and 20%. Finally, the response on HbF levels could be improved by an increase the HU dosage, from 20 mg/kg/day up to 35 mg/kg/day.

In all studies where it was evaluated, the frequency of VOC (Vaso-Occlusive Crises) decreased dramatically (by 66% to 80%), after the use of HU. The same dramatic response was observed for the number of hospital admissions and the number of days of hospitalisation. Finally, the number of ACS (Acute Chest Syndrome)/year decreased by 25 to 33%. Non-responders to the HU treatment reached 27% of the patients (children). The definitive clinical, pharmacodynamic or pharmacokinetic reasons underlying this non-response are unknown. A sustained clinical benefit was demonstrated for HU in patients remaining on treatment for up to 8 years.

The influence of the HU treatment on stroke has not been fully assessed by the Applicant. The applicant agreed that this should be done in the postmarketing surveillance Programme.

Quality of life data are sparse in adult clinical trials and absent in paediatric studies.

As the maximum dose of 40 mg/kg/day has only been evaluated in one study, the maximum therapeutic dose recommended is 35 mg/kg/day (under exceptional circumstances a maximum dose of 35 mg/kg b.w./day might be justified under close haematological monitoring, see SPC section 4.2). Moreover, the dose higher than 30 mg/kg/day should be exceptionally used, and only when there is a clearly increased clinical response to this dosage.

As only children older than 2 years have been followed in the main clinical studies, SPC recommendations about age in the section posology limit the use of HU to children older than 2 years.

©EMEA 2007

Clinical safety

- Patient exposure

Specifically the safety of hydroxycarbamide had been examined retroactively from cohorts of 123 adults and 352 paediatric patients, over 13 years and up to 12 years respectively.

- Adverse events

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 to diminish these effects (see section 4.2).

The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated form the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness:

Table 6. Adverse events

Blood and lymphatic system disorders:		
	Very common:	Bone marrow depression[1] including neutropenia (< 2.0 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
Gastrointestinal disorders:		
	Uncommon:	Nausea
	Not known:	Gastrointestinal disturbances, vomiting, gastrointestinal ulcer, severe hypomagnesaemia
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
	Not known:	Cutaneous dryness
Infections and infestations:		
	Not known:	Parvovirus B19 infection
Neoplasms, benign, malignant and unspecified		
	Not known:	Leukaemia and in elderly patients, skin cancers
Vascular disorders:		
	Not known:	Bleeding
General disorders and administration site conditions:		
	Not known:	Fever
Hepathobiliary disorders		
	Rare:	Elevated liver enzymes
Reproductive system and breast disorders:		
	Very rare:	Azoospermia, oligospermia[4]
	Not known:	Amenorrhea
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.

©EMEA 2007

[3] Mainly due to an infection with Parvovirus or a splenic sequestration.
[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] Which may be an effect of improved general conditions.

The clinical data obtained in patients with Sickle Cell Syndrome have not shown evidence of adverse effects of hydroxycarbamide on hepatic and renal function.

Additional adverse reactions associated with the use of hydroxycarbamide in the treatment of neoplastic diseases (doses usually above 40 mg/kg b.w./d) include hypersensitivity to the active substance, anorexia, hallucinations, disorientation, seizures, dizziness, acute pulmonary syndrome (diffuse pulmonary infiltrations, dyspnoea), allergic alveolitis, diarrhoea, constipation, maculo-papular rash, facial and peripheral erythema, skin cancer, actinic keratosis, leg ulcer, cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, hyperpigmentation, violet papules, skin and nail atrophy, scaling, dermatomyositis-like skin changes, pruritus, asthenia, dysuria, renal impairment, increased blood bilirubin, (transient) increased blood urea, blood uric acid and blood creatinine, fever, chills, malaise.

- Serious adverse event/deaths/other significant events

In the clinical trials, no deaths were attributed to HU .

RENAL TOXICITY. HU was not directly associated with any significant renal toxicity, but it has not been able to prevent the progression of renal damage which is an inevitable late feature of SCD.

HEPATIC TOXICITY. In a number of cases, administration of HU was associated with a slight elevation of the hepatic enzymes. This was reversible and did not cause any additional problems. However, this finding cannot always be ascribed solely to HU, as the fetal involvement is SCD is a common and unpredictable feature.

CUTANEOUS OR ORAL REACTIONS. These are already known from the long use of HU in haematological malignancies and were noted also in the SCD reports. Most of them, including ungual and cutaneous pigmentation, cutaneous xerosis, palmar-plantar keratoma, oral pigmentation, mouth ulcers, and ichthyosis were acceptable and did not require discontinuation of therapy; however, this was not the case with leg ulcers which are considered as a major side effect of the drug and led, at least in some instances to definitive or temporary discontinuation of therapy. Of course, here again the causative contribution of persisting venous stasis, capillary occlusion by the sickled red cells and inevitable skin infection cannot be ignored and make the evaluation of the toxicity of HU extremely difficult. There were no substantial differences with regards to dose of HU and severity of the above complications between adults and children.

LEUKEMOGENESIS; CARCINOGENICITY. Non- clinical experimental reports clearly associate HU with a number of chromosomal abnormalities; there also reports that patients with polycythemia vera or essential thrombocytocytosis treated with HU over several years have more probabilities of developing leukaemia in comparison to patients who have not received this medication. However, the occurrence of neoplastic disease in adult SCD patients who received HU over long periods of time was not higher than that of the control population. It is important to note that there is laboratory evidence of increased DNA mutations (illegitimate VDJ rearrangements or *ras* mutations) in HU-treated children, however, in a study of 26 children who had been exposed to HU for a period of 5 years and no child on HU acquired leukaemia (Hanft et al., 2000).Therefore, an increase in somatic mutations does not directly portrend leukaemia.

- Laboratory findings

Myelosuppression is the main adverse event encountered in the clinical trials, and is clearly linked to dosage of HU. The incidence of myelosuppression could reach 80% of patients at the maximal tolerated dose, while it occurred at a much lower incidence in the studies or patient registries in which HU dose was not increased until toxicity occurred.

LEUKOPENIA / NEUTROPENIA. This has been reported consistently in all studies. In most cases it occurred when the dose of HU exceeded the conventional daily dose of 20 mg/kg b.w.; however, in

©EMEA 2007

some cases it was unpredictably observed with lower doses, thus making blood counts mandatory every week at the beginning and bi-or tri-weekly thereafter. Leukopenia was promptly reversed on discontinuation of HU in all reported cases. In a couple of cases, considering the benefit of preventing the VOC crises, recurrent leukopenia led to splenectomy which allowed continuation of HU at a higher dose. Severe neutropenias leading to death have not been reported.

THROMBOCYTOPENIA. It occurred less frequently and has led to temporary discontinuation of therapy in a few cases only. In all reports thrombocytopenia was dose dependent and reversible upon discontinuation of HU.

APLASTIC ANEMIA. This has been reported in some studies and was reversible upon discontinuation of the drug. However, although search for a concomitant parvoviral or other infection did not disclose such a cause, the causative relation of HU cannot be conclusively assured.

- Safety in special populations

PREGNANCY

The literature contains reports of several women who conceived, and a few men who fathered children, after discontinuing a long treatment with HU; in none of these cases was any malformation or other fetal complication observed. This holds true also for the rare instances of SCD women who inadvertedly became pregnant while on the drug and continued gestation to term; here again, no congenital abnormalities or other complications were noticed. However, in this group, most pregnant women did not want to take the potential risks and elected termination of pregnancy.

- Safety related to drug-drug interactions and other interactions

No safety studies related to drug-drug interactions and other interactions have been submitted

- Post marketing experience

None available.

- Overdose

Acute mucocutaneous toxicity has been reported in patients receiving hydroxycarbamide at dosages 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, neutropenia was reported in isolated cases of hydroxycarbamide overdose (1.43 times and 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.

Discussion on clinical safety

Siklos is contraindicated in case of hypersensitivity to the active substance or to any of the excipients, severe hepatic (Child-Pugh classification C) or severe renal impairment (creatinine clearance < 30ml/min), toxic ranges of myelosuppression (as described in the SPC under section 4.2). Siklos is contraindicated during lactation.

The myelosuppression, which is the main adverse event encountered in the clinical trials, is clearly linked to the dosage of HU. The incidence of myelosuppression could reach 80% of the patients in the studies that attempted to reach MTD (maximal tolerated dose), while myelosuppression occurred at a much lower incidence in the studies or patient registries in which HU dose was not increased until toxicity occurred.

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 every two weeks 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.

©EMEA 2007

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 a preceding neutropenia. Recovery from myelosuppression is usually rapid when therapy is discontinued. Siklos therapy can then be re-initiated at a slightly lower dose (see section 4.2).

Siklos should be used with caution in patients with mild to moderate renal or hepatic impairment (see section 4.2).

Continuous follow-up of the growth of treated children is recommended.

It is difficult to obtain valid incidences of neoplasms in SCD patients, because of the small samples present in the studies. 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. In a study with patients suffering from Polycythaemia vera, the incidence of acute leukaemia after a median follow-up of 8.6 years was 5.9% in the HU group, as compared with 1.5% in the phlebotomy group. Somatic mutations were measured in 26 children who had been exposed to HU during 5 years. No child on HU acquired myelodysplasia, leukaemia, or any other malignancy. It is unknown whether this leukemogenic 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.

Reversible azo- and oligo-spermia have been rarely observed in man, although these disorders are also associated with the underlying disease (see 4.8, 5.3). Azoospermia and amenorrhoea are known complications of HU therapy. One case of azoospermia and one case of amenorrhoea have been reported in the paediatric clinical trials. The effects of HU on fertility have been emphasised in the SPC. These effects are considered as major events. The Applicant has agreed to seek protocol assistance in order to design an adequate protocol to investigate this issue.

As stroke is a major complication of SCD, it is difficult to ascertain a causal relationship between the occurrence of stroke and the use of HU. HU might even provide protection against stroke recurrence.

Hypersplenism and splenic sequestration are known complications of SCD. The incidence observed in clinical studies does not indicate a precipitation of these events by HU.

HU has a potential to precipitate leg ulcers in SCD patients with a history of ulcers. No definitive conclusion can be drawn about the influence of HU on this serious adverse event.

HU may prevent priapism attacks in SCD, probably at higher doses than usually prescribed for painful crisis prevention (25 to 35 mg/kg/day).

Some cases of ALT increase have been reported in the trials. However, no serious hepatic effects have been attributed to HU in patients with SCD.

In all studies to date, growth and development appear to be unaffected.

The data are too limited to justify any use of HU in pregnancy and lactation. However, no major adverse effect occurred in the newborns whose mother received HU during pregnancy.

The use of very high doses of HU should be avoided. The risk of major myelosuppression is considerably increased when HU is titrated up to the "maximum tolerated dose". The dosage of 30 mg/kg/day should only exceptionally be exceeded, i.e. when a better clinical response is observed with 35 mg/kg/day.

Concerning the long-term use of HU, which can be the rule in patients with SCD, while no cases with major adverse outcomes have been published, the following points remain a matter of concern:

- the effects of HU on growth,
- the risk of carcinogenic effects, and
- the use during pregnancy and lactation.

These three points are considered as major issues in the pharmacovigilance risk management plan.

©EMEA 2007

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

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.

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 antiretroviral agents 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.

Pregnancy: Studies in animals have shown reproductive toxicity (see section 5.3). Patients on hydroxycarbamide should be made aware of the theoretical risks to the foetus and those 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 outweighing the respective risk of hydroxycarbamide therapy against the switch to a blood transfusion programme.

Based on the limited amount of available information, in case of an exposure to hydroxycarbamide during pregnancy, a careful follow-up with adequate clinical, biological and ultrasonographic examinations should be considered.

Women of child-bearing potential should be advised to use adequate birth-control measures during treatment with hydroxycarbamide. The use of effective contraception is strongly recommended. If the patient becomes pregnant while taking Siklos, she should be advised of the potential risk to the foetus.

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

No studies on the effect on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported from literature, but not commonly. Patients should be advised not to drive or operate machines, if dizziness is experienced while taking Siklos.

2.5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The Marketing Authorisation Holder must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market. The Marketing Authorisation Holder commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance plan.

Risk Management Plan

The Applicant submitted a risk management plan to closely monitor the well-known toxicity of HU, not only the acute events (myelosuppression), but also the long-term effects, i.e. the potential

©EMEA 2007

carcinogenic effects, of which the importance and frequency remain unknown for children and adolescents treated with HU for SCD.

Table 7 Summary of the Risk Management Plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Myelosuppression, in particular neutropenia, particularly at maximum tolerated dosing	The frequency, severity, and outcome of myelosuppression (in particular, neutropenia) will be evaluated periodically within the Siklos Post- Marketing Authorisation Safety Follow-up	
Effect of hydroxycarbamide on fertility (spermatogenesis and spermatozoa function)	Male fertility will be assessed in a specific clinical study of volunteers providing semen for annual sperm analyses. These will be evaluated on a 2-yearly basis. A trend analysis will be prepared from the second biennial report.	
Skin ulceration and Vasculitis	Post-Marketing Authorisation Safety Follow-up	
Effect of hydroxycarbamide on breast-feeding and postnatal development of progeny	Post-Marketing Authorisation Safety Follow-up	
Long-term safety of hydroxycarbamide, in particular on the development of malignancies (especially leukaemia)	Post-Marketing Authorisation Safety Follow-up	
Safety of hydroxycarbamide in patients with underlying (SCD-related) hepatic or renal impairment	Post-Marketing Authorisation Safety Follow-up	
Amenorrhea	Case-series review based on spontaneous reporting and literature will be performed	
Influence of hydroxycarbamide in the prevention of SCD stroke	Post-Marketing Authorisation Safety Follow-up	
Influence of hydroxycarbamide on mortality	Post-Marketing Authorisation Safety Follow-up	
Influence of hydroxycarbamide in child and adolescent growth (end of puberty)	Post-Marketing Authorisation Safety Follow-up	See below
Influence of hydroxyurea in the prevention of SCD stroke	Post-Marketing Authorisation Safety Follow-up	
Influence of hydroxyurea on mortality	Post-Marketing Authorisation Safety Follow-up	
Concomitant use of nucleoside analogue reverse transcriptase inhibitors	Post-Marketing Authorisation Safety Follow-up	

©EMEA 2007

Concomitant use of hydroxycarbamide with other myelosuppressive agent or radiation therapy	Post-Marketing Authorisation Safety Follow-up	
Safety of hydroxycarbamide elderly patients	Post-Marketing Authorisation Safety Follow-up	

Summary of the EU Risk Management Plan

Safety Concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
MISSING INFORMATION		
Influence of hydroxycarbamide in child and adolescent growth (end of puberty)	… SIKLOS Cohort Follow-up: propose to conduct specific radiographies if the difference with the normal growth is upper to 2 standard deviation. Within the 2-yearly interim analyses arising from the SIKLOS Cohort Follow-up, sub-group analyses will be performed on these patients. An evaluation will be performed within the analyses as to whether these special populations have a significantly altered risk profile	Physician, nurse, etc. and patient' information via dedicated leaflets describing - how to treat children - the need of continuous follow-up of the growth of treated children. (special warning is the difference is upper to 2sd)

The CHMP, having considered the data submitted in the application, is of the opinion that additional risk minimisation activities are required beyond those included in the product information.

In particular, the Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe Siklos are provided with a physician information pack containing treatment guides for physicians and patients, containing agreed elements. For physicians, this includes the SPC, the need for periodic blood counts and dose adjustment, the need for contraception, the risk to male and female fertility, potential risk to foetus and breast feeding, the growth follow-up of treated children, the handling of broken tablets and the management of adverse drug reactions. The patient information pack should contain a number of key elements, including handling of broken tablets, need for periodic blood counts, information on crisis or infections, the patient information leaflet, the need for contraception, the risk to male and female fertility, potential risk to foetus and breast feeding, key signs and symptoms of serious adverse reactions, when to seek urgent attention from the health care provider and information on growth follow-up of treated children for their parents. The MAH must implement this educational plan nationally, prior to marketing, and as agreed with the competent authorities in the Member States. An updated Risk Management Plan should be provided as per the CHMP Guideline on Risk Management Systems for medicinal products of human use.

©EMEA 2007

Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

In the preclinical toxicity studies reviewed from the literature 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. In the human, according to a retrospective analysis of a cohort of 123 adult patients treated with hydroxycarbamide, twenty-three pregnancies have been reported from 15 women treated with hydroxycarbamide and partners of 3 men treated with hydroxycarbamide. Most (61 %) had a normal outcome with regard to term and normal birth. In the other cases with known evolution, pregnancy had been interrupted either voluntarily or upon medical advice. Thus the data on a limited number of exposed pregnancies indicate no adverse effects on pregnancy or on the health of the foetus/newborn. Due to the potential teratogenic effects in animal models, although no malformations have been reported in humans to date, the use of HU during pregnancy remains not recommended, although not contra-indicated.

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.

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.

In case the prescribed dosage 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 is discarded. Unused broken tablets must be replaced in blister and put back in the box. Anyone handling Siklos should wash ones hands before and after contact with the tablets.

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

Efficacy

In nearly all clinical studies reviewed from the literature conducted in patients with Sickle Cell Syndrome, hydroxycarbamide strongly reduced the frequency of vaso-occlusive episodes by 66% to 80%, in children and in adults. The same response was observed for the number of hospital admissions and the number of days of hospitalisation for patients treated with hydroxycarbamide. The yearly frequency of acute chest syndrome was also reduced by 25 to 33% under hydroxycarbamide in several studies. Acute chest syndrome is a frequent life-threatening complication of Sickle Cell Syndrome and is characterized 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 up to 8 years.

©EMEA 2007

The specific mechanism of action of hydroxycarbamide is not fully understood. One of the mechanisms by which hydroxycarbamide acts is the elevation of foetal haemoglobin (HbF) concentrations in sickle cell patients. HbF interferes with the polymerisation of HbS 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. This increase was highly significant at 6 months and the mean percentage HbF values was sustained at approximately 20% even after 7 years of continuous hydroxycarbamide therapy. The threshold of HbF for obtaining clinical efficacy could be comprised between 15 and 20%. The response on HbF levels could be improved by an increase the hydroxycarbamide dosage, from 20 mg/kg/day up to 35 mg/kg/day.

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.

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

Safety

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 to diminish these effects (see section 4.2). From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. Siklos is contraindicated in case of hypersensitivity to the active substance or to any of the excipients, severe hepatic (Child-Pugh classification C) or severe renal impairment (creatinine clearance < 30ml/min), toxic ranges of myelosuppression (as described in the SPC under section 4.2). Siklos is contraindicated during lactation.

The effect of the long-term use on male fertility and even more important the possible effect of this long term use in childhood on the development of sperm with a theoretical risk of inducing congenital physical defects, is not known. The Applicant has committed to investigate this issue and a protocol to study this has been presented in the Risk Management Plan. The applicant has considered the feasibilities to recruit a control group for the sperm study. The applicant agreed to seek scientific advice in order to find a better protocol that will lead to a data collection that will resolve this important issue.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

– User consultation

The Applicant submitted a readability testing report in accordance with the directive 2001/83/EC. The readability of the package leaflet has been assessed to ensure that potential users can locate, understand and appropriate act upon the information provided in the leaflet.

Risk-benefit assessment

Statistically and clinically significant reductions in pain episodes for the HU arm compared to placebo have been demonstrated. Other important benefits were a reduction in the frequency of hospitalisations and in total yearly days of hospitalisations. These improvements were not hampered by major toxic events. Acute toxic events (myelosuppression) could be minimized by the use of median doses (not exceeding 30 mg/kg/day). Long-term effects, including secondary malignancies, did not occur in the first 10 years of follow-up.

©EMEA 2007

No other pharmacological approach can be considered as a valuable alternative for HU. Repeated phlebotomy can reduce the frequency of painful episodes in selected patients with high steady state Hb levels. In pregnancy, prophylactic transfusion showed a decrease in painful episodes.

For patients with a history of severe or recurrent episodes of acute chest syndrome, HU therapy is recommended. Transfusion therapy is recommended if there is a clinical deterioration, multilobular infiltrates, or a history of underlying pulmonary or cardiac disease.

HU therapy can be considered to prevent recurrent events of stroke, although it has not been extensively studied.

The applicant committed to develop an additional pharmaceutical form, which is more adapted to children. Preliminary discussions with clinical experts have identified the 100 mg tablet form as the most appropriate dosage for these patients. The new dosage will be submitted within a maximum of two years after the granting of the marketing authorisation for Siklos 1000 mg tablets.

The potential risk of HU on long-term and short term is not negligible as HU is mitogenic and carcinogenic. An adequate risk management plan has been submitted.

The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns. Additional risk minimisation activities were required beyond those included in the product information. The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe Siklos are provided with physician information pack containing treatment guides for physicians and patients, containing agreed key elements. Furthermore, the Marketing Authorisation Holder must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market. The Marketing Authorisation Holder commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance plan. An updated Risk Management Plan should be provided as per the CHMP Guideline on Risk Management Systems for medicinal products of human use.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Siklos in the approved indication i.e. “prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in paediatric and adult patients suffering from symptomatic Sickle Cell Syndrome. (see section 5.1)” was favourable and therefore recommended the granting of the marketing authorisation.

©EMEA 2007