1. NAME OF THE MEDICINAL PRODUCT

Hydroxyurea 100 mg film-coated tablets
Hydroxyurea 1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Hydroxyurea 100 mg film-coated tablets
Each film-coated tablet contains 100 mg of hydroxyurea .

Hydroxyurea 1000 mg film-coated tablets
Each film-coated tablet contains 1000 mg of hydroxyurea.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

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

Hydroxyurea 1000 mg film-coated tablets
Off-white, capsule-shaped, film-coated tablet with triple scoring on both sides.
The tablet can be divided into four equal parts. Each quarter of tablet is embossed “T” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Hydroxyurea is indicated for the treatment of patients with:

- Chronic myeloid leukaemia (CML) in the chronic or accelerated phase of the disease.
- Essential thrombocythaemia or polycythaemia vera with a high risk of thromboembolic complications.

4.2 Posology and method of administration

Treatment must only be administered by a doctor experienced in oncology or haematology. The doses are based on the patient’s actual or ideal bodyweight, whichever is the less.

Posology
Symptomatic Sickle Cell Syndrome
The starting dose of hydroxyurea is 15 mg/kg b.w. and the usual dose is between 15 and 30 mg/kg b.w./day.

As long as the patient responds to therapy either clinically or haematologically (e.g. increase of haemoglobin F (HbF), Mean Corpuscular Volume (MCV), neutrophil count) the dose of Hydroxyurea 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 steps of 2.5 to 5 mg/kg b.w./day using the most appropriate strength.

Under exceptional circumstances a maximum dose of 35 mg/kg b.w./day might be justified under close haematological monitoring (see section 4.4). In the event a patient does still not respond when treated with the maximum dose of hydroxyurea (35 mg/kg b.w./day) over three to six months, permanent discontinuation of Hydroxyurea should be considered.

If blood counts are within the toxic range, Hydroxyurea 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 Hydroxyurea 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 $< 2 \times 10^9$/L
Platelets $< 80 \times 10^9$/L
Haemoglobin < 4.5 g/dL
Reticulocytes $< 80 \times 10^9$/L if the haemoglobin concentration < 9 g/dL

Long-term data on the continued use of hydroxyurea in patients with Sickle Cell Syndrome are available in children and adolescents, with a follow-up of 12 years in children and adolescents and over 13 years in adults. It is currently unknown how long patients should be treated with hydroxyurea. 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.

Chronic myeloid leukaemia
For CML, hydroxyurea is normally administered at an initial dose of 40 mg/kg b.w./day, depending on the white blood cell count. The dose is reduced by 50% (20 mg/kg b.w./day) if the white blood cell count drops below 20×10^9/L. The dose is then adjusted individually in order to maintain a white blood cell count of $5 - 10 \times 10^9$/L. The dose of hydroxyurea should be reduced if the white blood cell count drops below 5×10^9/L and increased if a white blood cell count of $>10 \times 10^9$/L is observed.

If the white blood cell count drops below 2.5×10^9/L, or the platelet count drops below 100×10^9/L, treatment should be discontinued until the counts significantly rise towards normal.

An adequate trial period to determine the antineoplastic effect of Hydroxyurea is six weeks. The treatment should be discontinued, if there is a significant progress of the disease. If there is a significant clinical response therapy may be continued indefinitely.

Essential Thrombocythaemia
In cases of essential thrombocythaemia, hydroxyurea is normally administered at an initial dose of 15 mg/kg/day and the dose is adjusted to maintain a platelet count of below 600×10^9/L, without lowering the white blood cell count below 4×10^9/L.

Polycythaemia vera
In cases of polycythaemia vera, hydroxyurea should be administered at an initial dose of 15-20 mg/ kg b.w./day. The hydroxyurea dose should be individually adjusted to keep the

haematocrit value below 45% and the platelet count below 400 x 10^9/L. For most patients this can be achieved through continuous administration of hydroxyurea with an average daily dose of 500 to 1000 mg. If the haematocrit value and the platelet count can be sufficiently controlled, treatment should be continued indefinitely.

Special populations

Paediatric population
Symptomatic Sickle Cell Syndrome
Because of the rarity of long-term data on treatment with hydroxyurea in children **less than 2 years of age**, dose regimens have not been established and thus, in this population, the treatment with hydroxyurea is not recommended.
Chronic myeloid leukaemia, Essential Thrombocythaemia and Polycythaemia vera
Because of the rarity of these conditions in children, dose regimens have not been established, the treatment with hydroxyurea is not recommended.

Doses for elderly patients
Elderly patients can be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen.

Renal impairment
Symptomatic Sickle Cell Syndrome
As renal excretion is a main pathway of elimination, dose reduction of Hydroxyurea should be considered in patients with renal impairment. In patients with a creatinine clearance ≤ 60 mL/min the initial Hydroxyurea dose should be decreased by 50%. Close monitoring of blood parameters is advised in these patients. Hydroxyurea must not be administered to patients with severe renal impairment (creatinine clearance < 30 ml/min) (see sections 4.3, 4.4 and 5.2).
CML, Essential Thrombocythaemia and Polycythaemia
No data are available. Dose recommendation cannot be given to patients with impaired renal function (see section 4.4).

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

Method of administration
Conforming to the individual dose, the tablet or the half or quarter 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.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Severe hepatic impairment (Child-Pugh classification C).
- Severe renal impairment (creatinine clearance < 30 mL/min).
- Toxic ranges of myelosuppression as described in section 4.2.

- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Treatment with Hydroxyurea 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 hydroxyurea, blood counts must be monitored every two weeks at treatment initiation (i.e. for the first two months) and if the daily dose of hydroxyurea is up to 35 mg/kg b.w. Patients who are stable on lower doses should be monitored every 2 months.

Treatment with Hydroxyurea 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. Hydroxyurea therapy can then be re-initiated at a lower dose (see section 4.2).

In cases of anaemia before or during ongoing treatment, red blood cells can be transfused if necessary. Also, severe anaemia can usually be corrected without interrupting hydroxyurea therapy. Self-limiting megaloblastic erythropoiesis is often observed early in treatment with hydroxyurea. The morphological changes are similar to pernicious anaemia but are not related to a vitamin B_{12} or folic acid deficiency.

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

Since there is no available data in patients with mild to moderate liver impairment, Hydroxyurea should be used with caution (see section 4.2).

Patients should be instructed to drink abundantly.

In patients with leg ulcers, Hydroxyurea should be used with caution. Leg ulcers are a common complication of Sickle Cell Syndrome, but have also been reported in patients treated with hydroxyurea. Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders during therapy with hydroxyurea. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease, hydroxyurea should be discontinued and/or its dose reduced if cutaneous vasculitic ulcerations develop. Rarely, ulcers are caused by leukocytoclastic vasculitis.

Erythema, atrophy of skin and nails, desquamation, violet papules, alopecia, dermatomyositis-like skin changes, actinic keratosis, skin cancer, lower leg ulcers, pruritus and hyperpigmentation of skin and nails have been observed in isolated cases after years of long-term daily maintenance therapy of hydroxyurea.

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

hydroxyurea causes macrocytosis, which may mask the incidental development of folic acid and vitamin B12 deficiency. Prophylactic administration of folic acid is recommended.

Hydroxyurea may aggravate the inflammation of mucous membranes secondary to irradiation. It can cause a recall of erythema and hyperpigmentation in previously irradiated tissues.

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

Patients should be advised to protect skin from sun exposure, conduct self-inspection of the skin and be screened for secondary malignancies during routine follow-up visits as squamous cell carcinoma has been observed in isolated instances.

Hydroxyurea may delay plasma iron clearance and reduce the rate of iron utilisation by erythrocytes but it does not appear to alter the red blood cell survival time.

In elderly patients the dose may need to be adjusted due to a higher sensitivity to hydroxyurea (see section 4.2).

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Specific interaction studies have not been performed with hydroxyurea.

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

Concurrent use of hydroxyurea 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 hydroxyurea.

Almost all patients receiving an adequate course of combined hydroxyurea and irradiation therapy will demonstrate concurrent leukopenia. Platelet depression (< 100,000 cells/mm^3) has occurred in the presence of marked leukopenia.

In vitro studies have demonstrated the ability of hydroxyurea to enhance the cytotoxicity in both cytarabine and fluoropyrimidines. It is unclear if this interaction leads clinically to cooperative toxicity or requires dose adjustment.

Concomitant use of hydroxyurea 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 hydroxyurea therapy. Vaccination with a live vaccine in a patient taking hydroxyurea may result in severe infections. Generally, the patient's antibody

response to vaccines may be decreased. Treatment with Hydroxyurea and concomitant immunisation with live virus vaccines should only be performed if benefits clearly outweigh potential risks.

4.6 Fertility, pregnancy and lactation

Hydroxyurea is genotoxic. Hydroxyurea has been demonstrated to be a potent teratogen in a wide variety of animal models. Embryo-foetal death, foetal malformation of the viscera and the skeleton, growth disorders and functional defects have been observed (see also section 5.3).

Women of childbearing potential/Contraception in males and females
Women of childbearing age receiving hydroxyurea should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur. An effective method of contraception is strongly recommended in women of childbearing potential. Male and female patients on hydroxyurea 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 hydroxyurea therapy against the switch to a blood transfusion programme.

Pregnancy
In the human, according to a retrospective analysis of a cohort of 123 adult patients treated with hydroxyurea, twenty-three pregnancies have been reported from 15 women treated with hydroxyurea and partners of 3 men treated with hydroxyurea. 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. Studies in animals have shown reproductive toxicity (see section 5.3). Patients on hydroxyurea should be made aware of the theoretical risks to the foetus.

Based on the limited amount of available information, in case of an exposure to hydroxyurea of pregnant female patients or pregnant partners of male patients, treated by hydroxyurea, a careful follow-up with adequate clinical, biological and ultrasonographic examinations should be considered.

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

Fertility
Fertility in males might be affected by treatment. Very common reversible oligo- and azoo-spermia have been observed in man, although these disorders are also associated with the underlying disease. Impaired fertility has been observed in male rats (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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 hydroxyurea. 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 hydroxyurea. Gradual dose titration may help to diminish these effects (see section 4.2).

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

Tabulated list of adverse reactions

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

Infections and infestations
Rare: Gangrene
Not known: Parvovirus B19 infection

Neoplasms, benign, malignant and unspecified
Not known: Leukaemia and skin cancer in elderly patients

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: Leukopenia, megaloblastosis, thrombocytopenia (< 80 x 10^9/L), anaemia (haemoglobin < 4.5 g/dl)[3]
Not known: CD4 lymphocytes decreased

Psychiatric Disorders
Very rare: Hallucination, disorientation

Nervous system disorders:
Common: Headache
Uncommon: Dizziness
Rare: Convulsions
Not known: Peripheral neuropathy

Respiratory, thoracic and mediastinal disorders
Rare: Acute pulmonary reactions consisting of diffuse pulmonary infiltrates and dyspnoea, fibrosis, allergic alveolitis

Vascular disorders:
Not known: Bleeding

Gastrointestinal disorders:
Common: Diarrhoea, constipation
Uncommon: Nausea, anorexia
Not known: Gastrointestinal disturbances, vomiting, gastrointestinal ulcer, severe hypomagnesaemia, pancreatitis, dyspepsia
Severe gastric stress (nausea, vomiting, anorexia) caused by a combination of hydroxyurea and radiation therapy can usually be controlled by temporarily interrupting treatment with hydroxyurea.

Renal and urinary disorders:
Uncommon: Transient impairment of renal tubular function accompanied by elevation of serum uric acid, urea and creatinine
Rare: Dysuria
Very rare: Renal impairment

Skin and subcutaneous tissue disorders:
Common: Skin reactions (for example oral, ungual and cutaneous pigmentation) and oral mucositis.
Uncommon: Rash, melanonychia, alopecia, facial erythema, acral erythema
Rare: Leg ulcers
Very rare: Systemic and cutaneous lupus erythematous, dermatomyositis-like skin changes, hyperpigmentation or atrophy of skin and nails, leg ulcers, pruritus, actinic keratosis, violet papules, desquamation
Not known: Cutaneous dryness, skin exfoliation

Metabolism and nutrition disorders
Rare: Tumour lysis syndrome

General disorders and administration site conditions Uncommon: Shivering, malaise Rare: Hypersensitivity reactions Not known: Fever, asthenia
Hepatobiliary disorders: Rare: Elevated liver enzymes Not known: Hepatotoxicity
Reproductive system and breast disorders: Very common: Oligospermia , azoospermia[4] Not known: Amenorrhea
Investigations: Not known: Weight gain[5]

[1] Haematological recovery usually occurs within two weeks of withdrawal of hydroxyurea.

[2] The macrocytosis caused by hydroxyurea is not vitamin B_{12} or folic acid dependent.

[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] Weight gain may be an effect of improved general conditions.

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

4.9 Overdose

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

In patients with Sickle Cell Syndrome, neutropenia was reported in isolated cases of hydroxyurea 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
The specific mechanism of action of hydroxyurea is not fully understood. One of the mechanisms by which hydroxyurea 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 hydroxyurea use.

Recently, hydroxyurea has shown to be associated with the generation of nitric oxide suggesting that nitric oxide stimulates cyclic guanosine monophosphatase (cGMP) production, which then activates a protein kinase and increases the production of HbF. Other known pharmacological effects of hydroxyurea which may contribute to its beneficial effects in Sickle Cell Syndrome include decrease of neutrophils, increase of the water content of erythrocytes, increase of the deformability of sickled cells, and altered adhesion of red blood cells to the endothelium.

In addition hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or protein. Cellular resistance is normally caused by increased ribonucleotide reductase levels as a result of gene amplification.

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

Clinical efficacy and safety
In nearly all clinical studies conducted in Sickle Cell Syndrome, hydroxyurea reduced the frequency of vaso-occlusive episodes by 66% to 80%, in children and in adults. The same decrease was observed for the number of hospital admissions and the number of days of hospitalisation in the treated groups. The yearly frequency of acute chest syndrome was also reduced by 25 to 33% under hydroxyurea in several studies. Acute chest syndrome is a frequent life-threatening complication of Sickle Cell Syndrome and is characterised by chest pain or fever or dyspnoea with recent infiltrate on chest X-ray.

A sustained clinical benefit was demonstrated in patients remaining on hydroxyurea treatment for up to 8 years.

5.2 Pharmacokinetic properties

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

Biotransformation
The biotransformation pathways as well as the metabolites are not fully characterised. Urea is one metabolite of hydroxyurea.

Hydroxyurea at 30, 100 and 300 µM is not metabolised in vitro by cytochrome P450s of human liver microsomes. At concentrations ranging from 10 to 300 µM, hydroxyurea does not stimulate the in vitro ATPase activity of recombinant human P glycoprotein (PGP), indicating that hydroxyurea is not a PGP substrate. Hence, no interaction is to be expected in case of concomitant administration with substances being substrates of cytochromes P450 or P-glycoprotein.

Elimination

In a repeated dose study in adult patients with Sickle Cell Syndrome approximately 60% of the hydroxyurea 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 hydroxyurea 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 hydroxyurea was eliminated with a half-life of approximately six to seven hours, which is longer than reported in other indications.

Geriatric, gender, race

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

Paediatric population

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

Renal impairment

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dose of Hydroxyurea in patients with renal impairment. In an open single-dose study in adult patients with Sickle Cell Syndrome (*Yan JH et al, 2005*) the influence of renal function on pharmacokinetics of hydroxyurea 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 hydroxyurea 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 hydroxyurea 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 hydroxyurea by 50% may be appropriate in patients with a CrCl ≤ 60 ml/min.

Haemodialysis reduced the exposure to hydroxyurea by 33% (see sections 4.2 and 4.4). Close monitoring of blood parameters is advised in these patients.

Hepatic impairment

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

5.3 Preclinical safety data

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

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

Hydroxyurea 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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium stearyl fumarate
Silicified microcrystalline cellulose
Basic butylated methacrylate copolymer

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

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

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with polypropylene child-resistant closure with a dessicant unit.
Hydroxyurea 100 mg film-coated tablets
Pack sizes of 60, 90 or 120 tablets.

Not all pack sizes may be marketed.

[Hydroxyurea] 1000 mg film-coated tablets Pack size of 30 tablets.

6.6 Special precautions for disposal and other handling

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

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

7. MARKETING AUTHORISATION HOLDER

Novartis Nigeria Limited

8. MARKETING AUTHORISATION NUMBER(S)

Hydroxyurea 100mg film-coated tablets - A4-100407
Hydroxyurea 1000mg film-coated tablets – A4-100408