

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Hydroxycarbamide 100 mg film-coated tablets

Hydroxyurea 100

Hydroxycarbamide 1000 mg film-coated tablets

Hydroxyurea 1000

2. Qualitative and quantitative composition

Hydroxyurea 100

Each film-coated tablet contains 100 mg of hydroxycarbamide.

Hydroxyurea 1000

Each film-coated tablet contains 1000 mg of hydroxycarbamide.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet

Hydroxyurea 100

White, round, film-coated tablet with one breaking notch on one side, on the same side debossment “|” on each half, plain on the other side.

Hydroxyurea 1000

White, oblong, film-coated tablet with three breaking notches on both sides, on one side debossment “|” on each of the 4 parts, no debossment on the other 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 (b.w.), whichever is the less.

Posology

Symptomatic Sickle Cell Syndrome

The starting dose of hydroxycarbamide is 15 mg/kg b.w. and the usual dose is between 15 and 30 mg/kg b.w./day.

As long as the patient responds to therapy either clinically or haematologically (e.g., increase of haemoglobin F (HbF), Mean Corpuscular Volume (MCV), neutrophil count), the dose of Hydroxyurea should be maintained.

In the 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 hydroxycarbamide (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 $< 4.5 \text{ g/dL}$

Reticulocytes $< 80 \times 10^9/L$ if the haemoglobin concentration $< 9 \text{ g/dL}$

Long-term data on the continued use of hydroxycarbamide in patients with Sickle Cell Syndrome are available in children and adolescents, with a follow-up of 12 years in children and adolescents and over 13 years in adults. It is currently unknown how long patients should be treated with 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, hydroxycarbamide 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 $20 \times 10^9/L$. 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 hydroxycarbamide should be reduced, if the white blood cell count drops below $5 \times 10^9/L$ and increased if a white blood cell count of $>10 \times 10^9/L$ is observed.

If the white blood cell count drops below $2.5 \times 10^9/L$, or the platelet count drops below $100 \times 10^9/L$, 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 significant progress of the disease. If there is a significant clinical response, therapy may be continued indefinitely.

Essential Thrombocythaemia

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

Polycythaemia vera

In the cases of polycythaemia vera, hydroxycarbamide should be administered at an initial dose of 15-20 mg/kg b.w./day. The hydroxycarbamide dose should be individually adjusted to keep the haematocrit value below 45% and the platelet count below $400 \times 10^9/L$. For most patients, this can be achieved through continuous administration of hydroxycarbamide 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 hydroxycarbamide in children **less than 2 years of age**, dose regimens have not been established and thus, in this population, the treatment with hydroxycarbamide 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 hydroxycarbamide is not recommended.

Doses for elderly patients

Elderly patients can be more sensitive to the effects of hydroxycarbamide 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 is 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

Haematological toxicities

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 hydroxycarbamide 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 the 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 the 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 hydroxycarbamide therapy. Self-limiting megaloblastic erythropoiesis is often observed early in the treatment with hydroxycarbamide. The morphological changes are similar to pernicious anaemia but are not related to a vitamin B₁₂ or folic acid deficiency.

Renal and hepatic impairment

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).

Leg ulcers and cutaneous vasculitis toxicities

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 hydroxycarbamide. Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders during therapy with hydroxycarbamide. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease, hydroxycarbamide should be discontinued and/or its dose reduced if cutaneous vasculitic ulcerations develop. Rarely, ulcers are caused by leukocytoclastic vasculitis.

Skin cancer

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 hydroxycarbamide. Hydroxycarbamide may

aggravate the inflammation of mucous membranes secondary to irradiation. It can cause a recall of erythema and hyperpigmentation in previously irradiated tissues. Continuous follow-up of the growth of treated children and adolescents is recommended.

Macrocytosis

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

Carcinogenicity

Hydroxycarbamide is unequivocally genotoxic in a wide range of test systems.

Hydroxycarbamide is presumed to be a trans-species carcinogen. In patients receiving long-term hydroxycarbamide for myeloproliferative disorders, secondary leukemia has been reported. 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.

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.

Interference with laboratory tests

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

Safe administration and monitoring

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

4.5 Interaction with other medicinal products and other forms of interaction

Specific interaction studies have not been performed with hydroxycarbamide.

Antiretrovirals

Potentially fatal pancreatitis and hepatotoxicity, and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxycarbamide in combination with antiretroviral medicinal products, particularly didanosine plus stavudine. Patients treated with hydroxycarbamide in combination with didanosine, stavudine, and indinavir showed a median decline in CD4 cells of approximately 100/mm³.

Myelosuppressive medicinal products or radiotherapy

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.

Almost all patients receiving an adequate course of combined hydroxycarbamide and irradiation therapy will demonstrate concurrent leukopenia. Platelet depression (< 100,000 cells/mm³) has occurred in the presence of marked leukopenia.

In vitro

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

Live virus vaccine

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. There is an increased risk of severe or fatal infections with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients (see section 4.4). 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

Hydroxycarbamide is genotoxic. Hydroxycarbamide 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).

Contraception in males and females

Male and female patients on hydroxycarbamide wishing to conceive should stop treatment 3 to 6 months before pregnancy if possible. The evaluation of the risk-benefit ratio should be made on an individual basis, outweighing the respective risk of hydroxycarbamide therapy against the switch to a blood transfusion programme.

Women of childbearing age receiving hydroxycarbamide should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur. An effective method of contraception is strongly recommended in women of childbearing potential.

Pregnancy

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. 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.

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

Breastfeeding

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

Fertility

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

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

Tabulated list of adverse reactions

The adverse reactions are listed below by system organ class and absolute frequency.

Frequencies are defined as very common ($\geq 1/10$), 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:

<i>Infections and infestations</i> Rare- Gangrene Not known- Parvovirus B19 infection
<i>Neoplasms, benign, malignant and unspecified</i> Not known- Leukaemia and skin cancer in elderly patients
<i>Blood and lymphatic system disorders</i> Very common- Bone marrow depression ¹ including neutropenia ($< 2.0 \times 10^9/L$), reticulocytopenia ($< 80 \times 10^9/L$), macrocytosis ² Common- Leukopenia, megaloblastosis, thrombocytopenia ($< 80 \times 10^9/L$), anaemia (haemoglobin < 4.5 g/dl) ³ Not known- CD4 lymphocytes decreased
<i>Psychiatric Disorders</i> Very rare- Hallucination, disorientation
<i>Nervous system disorders</i> Common- Headache Uncommon- Dizziness Rare- Convulsions Not known- Peripheral neuropathy

<p><i>Respiratory, thoracic and mediastinal disorders</i></p> <p>Rare- Acute pulmonary reactions consisting of diffuse pulmonary infiltrates and dyspnoea, fibrosis, allergic alveolitis</p>
<p><i>Vascular disorders</i></p> <p>Not known- Bleeding</p>
<p><i>Gastrointestinal disorders</i></p> <p>Common- Diarrhoea, constipation</p> <p>Uncommon- Nausea, anorexia</p> <p>Not known- Gastrointestinal disturbances, vomiting, gastrointestinal ulcer, severe hypomagnesaemia, pancreatitis, dyspepsia</p> <p>Severe gastric stress (nausea, vomiting, anorexia) caused by a combination of hydroxycarbamide and radiation therapy can usually be controlled by temporarily interrupting treatment with hydroxycarbamide.</p>
<p><i>Renal and urinary disorders</i></p> <p>Uncommon- Transient impairment of renal tubular function accompanied by elevation of serum uric acid, urea and creatinine</p> <p>Rare- Dysuria</p> <p>Very rare- Renal impairment</p>
<p><i>Skin and subcutaneous tissue disorders</i></p> <p>Common- Skin reactions (for example oral, ungual and cutaneous pigmentation) and oral mucositis.</p> <p>Uncommon- Rash, melanonychia, alopecia, facial erythema, acral erythema</p> <p>Rare- Leg ulcers</p> <p>Very rare- Systemic and cutaneous lupus erythematosus, dermatomyositis-like skin changes, hyperpigmentation or atrophy of skin and nails, leg ulcers, pruritus, actinic keratosis, violet papules, desquamation</p> <p>Not known- Cutaneous dryness, skin exfoliation</p>
<p><i>Metabolism and nutrition disorders</i></p> <p>Rare- Tumour lysis syndrome</p>
<p><i>General disorders and administration site conditions</i></p> <p>Uncommon- Shivering, malaise</p> <p>Rare- Hypersensitivity reactions</p> <p>Not known- Fever, asthenia</p>
<p><i>Hepatobiliary disorders</i></p> <p>Rare- Elevated liver enzymes</p> <p>Not known- Hepatotoxicity</p>
<p><i>Reproductive system and breast disorders</i></p> <p>Very common- Oligospermia , azoospermia⁴</p> <p>Not known- Amenorrhea</p>
<p><i>Investigations</i></p> <p>Not known- Weight gain⁵</p>

¹ Haematological recovery usually occurs within two weeks of withdrawal of hydroxycarbamide.

² The macrocytosis caused by hydroxycarbamide is not vitamin B₁₂ 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 e-PV desktop applications

(https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose

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

In patients with sickle cell syndrome, 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological classification: 31 Miscellaneous.

Mechanism of action

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.

Recently, hydroxycarbamide has shown to be associated with the generation of nitric oxide, suggesting that nitric oxide stimulates cyclic guanosine monophosphate (cGMP) production, which then activates a protein kinase and increases the production of HbF. Other known pharmacological effects of hydroxycarbamide which may contribute to its beneficial effects in Sickle Cell Syndrome include decrease 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, 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. Cellular resistance is normally caused by increased ribonucleotide reductase levels, as a result of gene amplification.

Pharmacodynamic effects

Besides 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.

Clinical efficacy and safety

In nearly all clinical studies conducted in Sick Cell Syndrome, hydroxycarbamide reduced the frequency of vaso-occlusive episodes by 40% to 80%, in children and in adults. The same decrease was observed for the number of hospital admissions and the number of days of hospitalisation in the treated groups. The yearly frequency of acute chest syndrome was also reduced by 25 to 68% under hydroxycarbamide in several studies. Acute chest syndrome is a frequent life-threatening complication of Sick Cell Syndrome and is characterised by chest pain or fever or dyspnoea with recent infiltrate on chest X-ray.

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

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Hydroxycarbamide distributes rapidly throughout the human body, enters the cerebrospinal fluid, appears in peritoneal fluid and ascites, and concentrates in leukocytes and erythrocytes. The estimated volume of distribution of hydroxycarbamide approximates total body water. The volume of distribution at the steady state adjusted for bioavailability is 0.57 L/kg in patients with Sick Cell Syndrome (amounting to approximately 72 and 90 L in children and adults, respectively). The extent of protein binding of hydroxycarbamide is unknown.

Biotransformation

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

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

Elimination

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

Geriatric, gender, race

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

Paediatric population

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

Renal impairment

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dose of 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 hydroxycarbamide was assessed. Patients with normal (creatinine clearance $\text{CrCl} > 80 \text{ mL/min}$), mild ($\text{CrCl} 60\text{--}80 \text{ mL/min}$), moderate ($\text{CrCl} 30\text{--}60 \text{ mL/min}$), or severe ($< 30 \text{ mL/min}$) 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 $\text{CrCl} < 60 \text{ mL/min}$ the area under the curve was approximately 51% higher than in patients with a $\text{CrCl} \geq 60 \text{ mL/min}$, which suggests that a dose reduction of hydroxycarbamide by 50% may be appropriate in patients with a $\text{CrCl} \leq 60 \text{ mL/min}$.

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

Hepatic impairment

There are no data that support specific guidance for dose adjustment in patients with hepatic impairment, but, due to safety considerations, 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.

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 trans-species 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 sternbrae, missing lumbar vertebrae.

Embryotoxicity was characterised by decreased foetal viability, reduced live litter sizes, and developmental delays.

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

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core

Silicified microcrystalline cellulose

Sucralose

Orange flavour

Sodium stearyl fumarate

Purified water

Film coat

Opadry II

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

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

The film-coated tablets are packed in high density polyethylene (HDPE) bottles with polypropylene (PP) screw caps with a desiccant (2g silica gel).

Hydroxyurea 100

Pack sizes of 30, 60, 90, 100, 200, 300 and 400 tablets.

Not all pack sizes may be marketed.

Hydroxyurea 1000

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 hydroxycarbamide. 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 the case that 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. APPLICANT

Sandoz SA (Pty) Limited
Waterfall 5-lr, Magwa Crescent West
Waterfall City
Jukskei View 2090
Gauteng
South Africa

8. MANUFACTURER

Haupt Pharma Amareg Gmbh
Donaustauer Strasse 378
D-93055 Regensburg
Germany

9. REGISTRATION DETAILS

Hydroxyurea 100

Zimbabwe registration number: 2023/31/6406
Zimbabwe category for distribution: Prescription Preparations (P.P.)

Hydroxyurea 1000

Zimbabwe registration number: 2023/31/6407
Zimbabwe category for distribution: Prescription Preparations (P.P.)

10. DATE OF REVISION OF THE TEXT

July 2023