SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hydroxycarbamide 500 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500 mg of Hydroxycarbamide.

Excipients with known effect:

Each capsule contains 41 mg of lactose.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

3 PHARMACEUTICAL FORM

Capsule, hard

Size 0 hard gelatin capsule, with an opaque pink body and an opaque light green cap, printed with black ink logo ‘HH3’, containing a homogeneous white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hydroxycarbamide is indicated in the treatment of patients with:

- chronic myeloid leukaemia (CML) in chronic or accelerated phase.
- essential thrombocythemia or polycythemia vera with high risk for thromboembolic complications.

4.2 Posology and method of administration

Hydroxycarbamide therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. Dosage should be based on the patient's actual or ideal weight, whichever is the less. Therapy should be monitored by repeat blood counts.

Posology

Adults
In CML hydroxycarbamide is usually given at an initial dose of 40 mg/kg daily dependent on the white cell count. The dose is reduced by 50 % (20 mg/kg daily) when the white cell count is dropped below 20 x 10^9/l. The dose is then adjusted individually to keep the white cell count at 5 – 10 x 10^9/l. Hydroxycarbamide dose should be reduced if white cell counts fall below 5 x 10^9/l and increased if white cell counts > 10 x 10^9/l are observed.

If white cell count falls below 2.5 x 10^9/l, or the platelet count below 100 x 10^9/l, therapy should be interrupted until the counts rise significantly towards normal. In this situation white blood cell count and platelet should be monitored at least every 3 days.

An adequate trial period for determining the antineoplastic effect of hydroxycarbamide is six weeks. Where there is a significant clinical response therapy may be continued indefinitely, provided that the patient is kept under adequate observation and shows no unusual or severe reactions.

In essential thrombocythemia hydroxycarbamide is usually given at starting doses of 15 mg/kg/day with dose adjustment to maintain a platelet count below 600 x 10^9/l without lowering the white blood cell count below 4 x 10^9/l.

In polycythemia vera hydroxycarbamide should be started at a dosage of 15 – 20 mg/kg/day. Hydroxycarbamide dose should be adjusted individually to maintain the hematocrit below 45 % and platelet count below 400 x 10^9/l. In most patients this can be achieved with hydroxycarbamide given continuously at average daily doses of 500 to 1000 mg.

Concurrent use of hydroxycarbamide with other myelosuppressive agents may require adjustments of dosages.

Paediatric population
Because of the rarity of these conditions in children, dosage regimens have not been established.

Elderly
Elderly patients may be more sensitive to the effects of hydroxycarbamide and may require a lower dosage regimen.

Renal impairment
As renal excretion is a main pathway of elimination, dose reduction of hydroxycarbamide should be considered in patients with renal impairment. In patients with a creatinine clearance ≤ 60 ml/min the initial hydroxycarbamide dose should be decreased by 50%. Close monitoring of blood parameters is advised in these patients. (see sections 4.4 and 5.2).

Hepatic impairment
There are no data that support specific dose adjustments in patients with hepatic impairment. Close monitoring of blood parameters is advised in these patients.

Method of administration
For oral use

NB: If the patient prefers, or is unable to swallow capsules, the contents of the capsules may be emptied into a glass of water and taken immediately. Patients should be instructed to drink abundantly. The contents of capsules should not be inhaled or allowed to come into contact with the skin or mucous membranes. Spillages must be wiped immediately.

4.3 Contraindications

Hydroxycarbamide is contraindicated in the following cases:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Marked leucopenia (<2.5wbc x 10^9/L), thrombocytopenia (< 100 x 10^9/L) or severe anaemia.

4.4 Special warnings and precautions for use

Treatment with Hydroxycarbamide 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. The determination of haemoglobin level, total leukocyte counts, and platelet counts should be performed at least once a week throughout the course of hydroxycarbamide therapy. If WBC falls below 2.5x10^9/L or platelet count to <100x10^9/L, therapy should be interrupted. Counts should be rechecked after 3 days and treatment resumed when they rise significantly towards normal.

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

Severe anaemia must be corrected with whole blood replacement before initiating therapy with hydroxycarbamide. If, during treatment, anaemia occurs, correct without interrupting hydroxycarbamide therapy. Erythrocytic abnormalities; megaloblastic erythropoeisis, which is self-limiting, is often seen early in the course of hydroxycarbamide therapy. The morphologic change resembles pernicious anaemia, but is not related to vitamin B12 or folic acid deficiency. However, as the occurrence of macrocytosis can mask the occurrence of folic acid deficiency, prophylactic administration of folic acid is indicated in such situations. Hydroxycarbamide may also delay plasma iron clearance and reduce the rate of iron utilisation by erythrocytes but it does not appear to alter the red blood cell survival time.

Cases of hemolytic anemia in patients treated with hydroxycarbamide for myeloproliferative diseases have been reported. Patients who develop severe anemia

should have laboratory tests evaluated for hemolysis. If diagnosis of hemolytic anemia is established, hydroxycarbamide should be discontinued.

Hydroxycarbamide should be used with caution in patients with mild to moderate renal impairment and, since there is no available data, also in patients with mild to moderate liver impairment. (see section 4.2).

Elderly patients may be more sensitive to the effects of hydroxycarbamide and may require a lower dosage regimen (see section 4.2).

The possibility of an increase in serum uric acid, resulting in the development of gout or, at worst, uric acid nephropathy, should be borne in mind in patients treated with hydroxycarbamide, especially when used with other cytotoxic agents. It is therefore important to monitor uric acid levels regularly and maintain a high fluid intake during treatment.

Hydroxycarbamide is not licensed for use in combination with antiretroviral agents for HIV disease and it may cause treatment failure and toxicities (in some cases fatal) in HIV patients (see section 4.5).

In patients receiving long-term therapy with hydroxycarbamide for myeloproliferative disorders, such as polycythemia, secondary leukaemia has been reported. It is unknown whether this leukaemogenic effect is secondary to hydroxycarbamide or associated with the patient's underlying disease.

Hydroxycarbamide can induce painful leg ulcers which are usually difficult to treat and require cessation of therapy. Discontinuation of hydroxycarbamide usually leads to slow resolution of the ulcers over some weeks.

Cutaneous vasculitic toxicities including vasculitic ulcerations and gangrene have occurred in patients with myeloproliferative disorders during therapy with hydroxycarbamide. The risk of vasculitic toxicities is increased in patients who receive prior or concomitant interferon therapy. The digital distribution of these vasculitic ulcerations and progressive clinical behaviour of peripheral vasculitic insufficiency leading to digital infarct or gangrene were distinctly different than the typical skin ulcers generally described with Hydroxycarbamide. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease, hydroxycarbamide should be discontinued if cutaneous vasculitic ulcerations develop and alternative cytoreductive agents should be initiated as indicated.

Hydroxycarbamide is unequivocally genotoxic in a wide range of test systems. Hydroxycarbamide is presumed to be a transspecies carcinogen.
The monitoring of skin changes is advisable during hydroxycarbamide treatment as in single cases squamous cell carcinoma of the skin was reported.

Skin cancer has been reported in patients receiving long-term hydroxycarbamide. Patients should be advised to protect skin from sun exposure. In addition, patients should conduct self inspection of the skin during the treatment and after

discontinuation of the therapy with hydroxycarbamide and be screened for secondary malignancies during routine follow-up visits.

Respiratory disorders:
Interstitial lung disease including pulmonary fibrosis, lung infiltration, pneumonitis, and alveolitis/allergic alveolitis have been reported in patients treated for myeloproliferative neoplasm and may be associated with fatal outcome. Patient developing pyrexia, cough, dyspnoea or other respiratory symptoms should be closely monitored, investigated and treated. Promptly discontinue of hydroxyurea and treatment with corticosteroids appears to be associated with resolution of the pulmonary events (see section 4.8).

This medicine contains lactose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains sodium.
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Specific interaction studies have not been performed with hydroxycarbamide. 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.

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/mm^3.

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 defense mechanisms may be suppressed by hydroxycarbamide therapy. Vaccination with a live vaccine in a patient taking hydroxycarbamide may result in severe infections. Generally, the patient's antibody response to vaccines may be decreased. Treatment with Hydroxycarbamide and concomitant immunisation with live virus vaccines should only be performed if benefits clearly outweigh potential risks.

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy
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. 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 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.

Breast-feeding
Hydroxycarbamide is excreted in human milk. Because of the potential for serious adverse reactions in infants from hydroxycarbamide, a decision should be made whether to discontinue nursing or to discontinue Hydroxycarbamide, taking into account the importance of the drug to the mother.

Fertility
Fertility in males might be affected by treatment. Reversible azo- and oligo-spermia have been rarely 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

Ability to react may be impaired during treatment with Hydroxycarbamide. This should be born in mind when heightened attention is required, e.g for driving and using machines.

4.8 Undesirable effects

Bone marrow depression is the dose limiting toxicity. Gastrointestinal side effects are common but require rarely dose reduction or cessation of treatment.

Adverse event frequencies have been categorised as follows:

- 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 from the available data).

System Organ Class	Frequency	MedDRA Term
Infections and Infestations	Rare	Gangrene
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Skin cancer
Blood and lymphatic system disorders	Very common	Bone marrow failure, CD4 lymphocytes decreased, leukopenia, thrombocytopenia, anaemia
	Common	Megaloblastosis
	Not known	Hemolytic anemia
Metabolism and nutrition disorders	Very common	Anorexia
	Not known	Weight gain
Psychiatric disorders	Common	Hallucination, disorientation
Nervous system disorders	Common	Convulsion, dizziness, peripheral neuropathy[1], somnolence, headache
Respiratory, thoracic and mediastinal disorders	Common	Pulmonary fibrosis, pulmonary oedema, lung infiltration, dyspnoea
	Rare	Allergic alveolitits
	Not known	Interstitial lung disease, pneumonitis, alveolitis, cough
Gastrointestinal disorders	Very common	Pancreatitis[1], nausea, vomiting, diarrhoea, stomatitis, constipation, mucositis, stomach discomfort, dyspepsia, abdominal pain, melaena
Hepatobiliary disorders	Common	Hepatotoxicity[1], hepatic enzyme increased, cholestasis, hepatitis
	Uncommon	Jaundice
Skin and subcutaneous tissue disorders	Very common	Cutaneous vasculitis, dermatomyositis, alopecia, rash maculo-papular, rash papular, skin exfoliation, skin atrophy, skin ulcer, erythema, skin hyperpigmentation, nail disorder

	Very rare	Systemic and cutaneous lupus erythematous
	Not known	Porphyria cutanea tarda
Musculoskeletal and connective tissue disorders	Not known	Muscle pain
Renal and Urinary Disorders	Very common	Dysuria, blood creatinine increased, blood urea increased, blood uric acid increased
	Not known	Micturition problems, kidney failure
Reproductive system and breast disorders	Very common	Azoospermia, oligospermia
	Not known	Gynecomastia
General disorders and administration site conditions:	Very common	Pyrexia, asthenia, chills, malaise
	Rare	Hypersensitivity reaction

[1]Fatal and non-fatal pancreatitis and hepatotoxicity and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxyurea in combination with antiretroviral agents, in particular didanosine plus stavudine.

Blood and lymphatic system disorders:
In the therapy with hydroxycarbamide megaloblastosis may occur which does not respond to treatment with folic acid or B_{12}. The bone-marrow suppression subsides, however, when therapy is discontinued.
Hydroxycarbamide can reduce plasma iron clearance and iron utilisation by erythrocytes. However, it does not appear to alter the red blood cell survival time.

Gastrointestinal disorders:
Severe gastric distress (nausea, emesis, anorexia) resulting from combined hydroxycarbamide and irradiation therapy may usually be controlled by temporarily discontinuing hydroxycarbamide administration.

Skin and subcutaneous tissue disorders:
Hydroxycarbamide may aggravate the inflammation of mucous membranes secondary to irradiation. It can cause a recall of erythema and hyperpigmentation in previously irradiated tissues.
Erythema, atrophy of skin and nails, desquamation, alopecia, dermatomyositis-like skin changes, skin cancer, cutaneous ulcers (especially leg ulcers) and hyperpigmentation of skin and nails have been observed in isolated cases partly after years of long-term daily maintenance therapy with hydroxycarbamide.

Nervous system disorders:
High doses may cause moderate drowsiness.

Neoplasms benign, malignant and unspecified (incl cysts and polyps):
In patients receiving long-term treatment with hydroxycarbamide for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia may develop. To what extent this relates to the underlying disease or to treatment with hydroxycarbamide is presently unknown.

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 Yellow Card Scheme, at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Immediate treatment consists of gastric lavage, followed by supportive therapy for the cardiorespiratory systems if required. In the long term, careful monitoring of the haemopoietic system is essential and, if necessary, blood should be transfused.

Acute mucocutaneous toxicity has been reported in patients receiving hydroxycarbamide at a dosage several times greater than that recommended. Soreness, violet erythema, oedema on palms and foot soles followed by scaling of hands and feet, intense generalised hyperpigmentation of skin, and severe acute stomatitis were observed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents/other antineoplastic agents, ATC Code: L01XX05

Hydroxycarbamide is an orally active antineoplastic agent. Although the mechanism of action has not yet been clearly defined, hydroxycarbamide appears to act by interfering with synthesis of DNA.

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. 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.

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

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

Elimination
In 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.

Mean cumulative urinary hydroxycarbamide excretion was 35–40% in cancer patients.

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

Renal impairment
As renal excretion is a pathway of elimination, consideration should be given to decreasing the dose of hydroxycarbamide in patients with renal impairment. Patients with normal (creatinine clearance CrCl>80 ml/min), mild (CrCl 60–80 ml/min), moderate (CrCl 30 - 60 ml/min), or severe (<30 ml/min) renal impairment received hydroxycarbamide as a single dose of 15 mg/kg b.w. by using 200 mg, 300 mg, or 400 mg capsules. In patients, whose CrCl was below 60 ml/min or patients with end-stage renal disease the mean exposure to hydroxycarbamide was approximately 64% higher than in patients with normal renal function.
As evaluated in a further study, in patients with a CrCl<60 ml/min the area under the curve was approximately 51% higher than in patients with a CrCl ≥60 ml/min, which suggests that a dose reduction of hydroxycarbamide by 50% may be appropriate in patients with a CrCl < 60 ml/min.
Haemodialysis reduced the exposure to hydroxycarbamide by 33% (see sections 4.2 and 4.4).
Close monitoring of blood parameters is advised in these patients.

Hepatic impairment
There are no data that support specific guidance for dose adjustment in patients with hepatic impairment. Close monitoring of blood parameters is advised in patients with hepatic impairment.

5.3 Preclinical safety data

In preclinical toxicity studies the most common effects noted included bone marrow depression, lymphoid atrophy and degenerative changes in the epithelium of the small and large intestines.

Cardiovascular effects and haematological changes were observed in some species. Also, in rats testicular atrophy with decreased spermatogenesis occurred, while in dogs reversible spermatogenic arrest was noted.

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Lactose monohydrate
Magnesium stearate
Disodium phosphate anhydrous

Hard capsules contain:
Gelatin, E441
Erythrosine, E127
Titanium dioxide, E171
Black iron oxide, E172 (i)
Patent blue V, E 131
Yellow iron oxide, E172 (iii)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

30, 50 or 100 capsules packaged in PVC/aluminium blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

People who are not taking Hydroxycarbamide should not be exposed to it. To decrease the risk of exposure, wear disposable gloves when handling Hydroxycarbamide. Anyone handling Hydroxycarbamide should wash their hands before and after contact with the capsules. Pregnant women should not handle Hydroxycarbamide.

To minimise the risk of dermal exposure, always wear impervious gloves when handling capsules containing hydroxycarbamide. This includes all handling activities in clinical settings, pharmacies, storerooms and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration. Local guidelines on handling cytotoxics should always be followed.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 15413/0130

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/03/2021

10 DATE OF REVISION OF THE TEXT

17/03/2023