

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hydrea 500 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 500 mg hydroxycarbamide.

Excipients with known effect

Each hard capsule contains 40.1 mg of lactose (as monohydrate) and 11.7 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard.

Size 0 hard gelatin capsule with an opaque pink body and an opaque green cap, containing a white homogeneous powder. Printed with 'CHP 500' in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the management of malignant neoplastic disease including chronic myeloid leukaemia (pretreatment phase and palliative care). It is also indicated for treatment of cancer of the cervix and other solid type tumours in conjunction with radiotherapy.

4.2 Posology and method of administration

Posology

Treatment regimens can be continuous or intermittent. The continuous regimen is particularly suitable for chronic myeloid leukaemia, while the intermittent regimen, with its diminished effect on the bone marrow, is more satisfactory for the management of solid type tumours.

An adequate trial period for determining the antineoplastic effect of Hydrea 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. Therapy should be interrupted if the white cell count drops below $2.5 \times 10^9/L$ or the platelet count below $100 \times 10^9/L$ (see section 4.4). In these cases, the counts should be re-evaluated after three days and therapy resumed when the counts return to acceptable levels. Hematopoietic rebound is usually rapid. If rapid rebound has not occurred during combined Hydrea and irradiation therapy, irradiation may also be interrupted. Anaemia, even if severe, can be managed without interrupting Hydrea therapy.

Continuous therapy

20-30 mg/kg Hydrea should be given daily in single doses. Dosage should be based on the patient's actual or ideal weight, whichever is the less. Therapy should be monitored by repeat blood counts.

Intermittent therapy

80 mg/kg Hydrea in single doses should be given every third day. Using the intermittent regimes the likelihood of WBC depression is diminished, but if low counts are produced, 1 or more doses of Hydrea should be omitted.

Hydrea should be started 7 days before concurrent irradiation therapy. If Hydrea is used concomitantly with radiotherapy, adjustment of radiation dosage is not usually necessary.

Concurrent use of Hydrea with other myelosuppressive agents may require adjustments of dosages (see section 4.5).

Special Populations

Elderly

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

Children

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

Renal Impairment

Since renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of Hydrea in this population. Careful monitoring of the patient's hematological parameters is advised (see section 4.4).

Hepatic impairment

No dosage recommendation can be given. Careful monitoring of the patient's hematological parameters is advised (see section 4.4).

Method of administration

Oral

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. Some inert material used as a vehicle in the capsule may not dissolve and float on the surface. 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.

See section 6.6 for precautions on handling the medicinal product.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Marked leukopenia ($<2.5\text{WBC}\times 10^9/\text{L}$), thrombocytopenia ($<100\times 10^9/\text{L}$), or severe anaemia. Use in non-malignant disease.

4.4 Special warnings and precautions for use

Hydroxycarbamide should only be administered under the direction of a specialist oncology service having the facilities for regular monitoring of clinical biochemical and haematological effects during and after administration.

Renal and hepatic impairment

During treatment, regular checks of blood counts and liver and kidney function are necessary. Experience from treatment of patients with impaired hepatic and/or renal function is limited, and caution should therefore be exercised, especially at the start of treatment (see section 4.2).

Bone Marrow

The complete status of the blood, including bone marrow examination, if indicated, as well as kidney function and liver function should be determined prior to, and repeatedly during, treatment. If bone marrow function is depressed, treatment with Hydrea should not be initiated. 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 $2.5\times 10^9/\text{L}$ or Platelet count to $<100\times 10^9/\text{L}$, therapy should be interrupted. Counts should be rechecked after 3 days and treatment resumed when they rise significantly towards normal.

Hydrea may produce bone marrow suppression; leukopenia is generally its first and most common manifestation.

Thrombocytopenia and anaemia occur less often and are seldom seen without a preceding leukopenia. Bone marrow depression is more likely in patients who have previously received radiotherapy or cytotoxic cancer chemotherapeutic agents; Hydrea should be used cautiously in such patients (see section 4.5). The recovery from myelosuppression is rapid when Hydrea therapy is interrupted.

Anaemia

Severe anaemia must be corrected with whole blood replacement before initiating therapy with hydroxycarbamide. If, during treatment, anaemia occurs, correct without interrupting Hydrea therapy. Erythrocytic abnormalities; megaloblastic erythropoiesis, 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. The macrocytosis may mask the incidental development of folic acid deficiency; regular determinations of serum folic acid are recommended.

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 haemolytic anaemia in patients treated with Hydrea for myeloproliferative diseases have been reported (see section 4.8). Patients who develop persistent anaemia should have laboratory tests evaluated for haemolysis. In the setting of confirmed diagnosis of haemolytic anaemia, Hydrea should be discontinued.

Irradiation

Patients who have received irradiation therapy in the past may have an exacerbation of post irradiation erythema when Hydrea is given.

Pain or discomfort from inflammation of the mucous membranes at the irradiated site (mucositis) is usually controlled by measures such as topical anesthetics and orally administered analgesics. If the reaction is severe, Hydrea therapy may be temporarily interrupted; if it is extremely severe, irradiation dosage may, in addition, be temporarily postponed. Severe gastric distress, such as nausea, vomiting, and anorexia, resulting from combined therapy may usually be controlled by interruption of Hydrea administration.

Uric acid

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.

Vasculitis toxicities

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 if cutaneous vasculitic ulcerations develop and alternative cytoreductive agents should be initiated as indicated.

Cancer

Hydroxycarbamide has been shown to be carcinogenic in animals. The possibility of a similar effect should be borne in mind when designing the long-term management of the patient.

In patients receiving long-term hydroxycarbamide for myeloproliferative disorders, such as polycythaemia vera and thrombocythemia, secondary leukaemia has been reported; it is unknown whether this leukemogenic effect is secondary to hydroxycarbamide or the patient's underlying disease. 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. Other forms of treatment should be considered if skin cancer or epithelial dysplasia is diagnosed. In such cases, the dermatological monitoring should continue after treatment with hydroxycarbamide is discontinued.

Vaccinations

Concomitant use of Hydrea with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase some of the adverse reaction of the vaccine virus because normal defence mechanisms may be suppressed by Hydrea. Vaccination with a live vaccine in a patient taking Hydrea may result in severe infection. The patient's antibody response to vaccines may be decreased. The use of live vaccines should be avoided during treatment and for at least six months after treatment has finished and individual specialist advice sought (see section 4.5).

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. Patients developing pyrexia, cough, dyspnoea or other respiratory symptoms should be closely monitored, investigated and treated. Prompt discontinuation of hydroxycarbamide and treatment with corticosteroids appears to be associated with resolution of the pulmonary events (see section 4.8).

Interference with Continuous Glucose Monitoring Systems

Hydroxycarbamide may falsely elevate sensor glucose results from certain continuous glucose monitoring (CGM) systems which may lead to hypoglycaemia if sensor glucose results are relied upon to dose insulin.

If CGM systems are to be used concurrently with hydroxycarbamide treatment, consult with the CGM prescriber about the need to consider alternative glucose monitoring methods.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicine contains 11.7 mg sodium per capsule, equivalent to 0.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use of hydroxycarbamide and other myelosuppressive agents or radiotherapy can increase the likelihood of bone marrow impairment or other adverse effects (see section 4.2, 4.4 and 4.8).

Fatal and non-fatal pancreatitis, hepatotoxicity, hepatic failure and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxycarbamide in combination with antiretroviral agents, in particular didanosine with or without stavudine. Fatal hepatic events were reported most often in patients treated with the combination of hydroxycarbamide, didanosine, and stavudine. This combination should be avoided. Patients treated with hydroxycarbamide in combination with didanosine, stavudine, and indinavir in study ACTG 5025 showed a median decline in CD4 cells of approximately 100/mm³.

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.

Vaccinations

There is increased risk of fatal systemic vaccine disease with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients (see section 4.4).

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4.6 Fertility, pregnancy and lactation

Pregnancy

Hydrea can cause fetal harm when administered to a pregnant woman. Hydrea should not normally be administered to patients who are pregnant, or to mothers who are breast feeding, unless the potential benefits outweigh the possible hazards.

Drugs which affect DNA synthesis, such as hydroxycarbamide, may be potent mutagenic agents. The physician should counsel both male and female patients to use effective contraception during and after therapy as per the time periods specified below. Since Hydrea is a cytotoxic agent it has produced a teratogenic effect in some animal species.

Breastfeeding

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

Fertility

In rats and dogs, high doses of hydroxycarbamide reduced sperm production.

When appropriate both male and female patients should be counselled concerning the use of effective contraceptive measures before and during treatment with Hydrea.

Azoospermia or oligospermia, sometimes reversible, have been observed in men. Male patients should be informed about the possibility of sperm conservation before the start of therapy.

Hydroxycarbamide may be genotoxic. Men under therapy are advised to use safe contraceptive measures during and at least 3 months after therapy.

Female patients of reproductive potential should be counselled to use effective contraception during therapy and for at least 6 months after therapy.

4.7 Effects on ability to drive and use machines

Hydroxycarbamide may cause drowsiness. Patients receiving it should not drive or operate machinery unless it has been shown not to affect physical or mental ability.

4.8 Undesirable effects

Description of selected adverse reactions

Bone-marrow suppression is the major toxic effect of hydroxycarbamide.

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.

In some patients, hyperpigmentation, nail pigmentation, atrophy of skin and nails, scaling, violet papules and alopecia have been observed following several years of long-term daily maintenance therapy with hydroxycarbamide.

Cases of fatal and non-fatal pancreatitis and hepatotoxicity and severe peripheral neuropathy have been observed in HIV patients when hydroxycarbamide was administered with antiretroviral agents, in particular 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 (see sections 4.4 and 4.5).

Adverse reactions observed with combined Hydrea and irradiation therapy were similar to those reported with the use of Hydrea alone, primarily bone marrow depression (leukopenia and anaemia) and gastric irritation. Nearly all patients receiving an adequate course of combined Hydrea and irradiation therapy will develop leukopenia. Decreased platelet counts (<100,000/mm³) have occurred rarely and usually in the presence of marked leukopenia. Hydrea may potentiate some adverse reactions usually seen with irradiation alone, such as gastric distress and mucositis.

Hypersensitivity

Drug induced fever

High fever (>39°C) requiring hospitalisation in some cases has been reported concurrently with gastrointestinal, pulmonary, musculoskeletal, hepatobiliary, dermatological or cardiovascular manifestations. Onset typically occurred within 6 weeks of initiation and resolved promptly after discontinuation of hydroxycarbamide. Upon readministration fever re-occurred within 24 hours.

The list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000), and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Reaction (MedDRA Term)
Infections and Infestations	Rare	Gangrene
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	Common	Skin cancer
Blood and Lymphatic System Disorders	Very common	Bone marrow impairment, CD4 lymphocytes decreased, leukopenia, thrombocytopenia, platelet count decreased, anaemia
	Not Known	Haemolytic anaemia
Metabolism and Nutrition Disorders	Very common	Anorexia
	Rare	Tumour lysis syndrome
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

	Not known	Interstitial lung disease, pneumonitis, alveolitis, allergic 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
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	Cutaneous lupus erythematosus
	Not known	Nail pigmentation
Musculoskeletal and Connective Tissue Disorders	Very rare	Systemic lupus erythematosus
Renal and Urinary Disorders	Very common	Dysuria, blood creatinine increased, blood urea increased, blood uric acid increased
Reproductive System and Breast Disorders	Very common	azoospermia, oligospermia
General Disorders and Administration Site Conditions	Very common	Pyrexia, asthenia, chills, malaise
	Not known	Drug-induced fever
1 Fatal and non-fatal pancreatitis and hepatotoxicity and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxycarbamide in combination with antiretroviral agents, in particular didanosine plus stavudine.		

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

HPRA Pharmacovigilance

Website: www.hpra.ie

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 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

After oral administration hydroxycarbamide is readily absorbed from the gastrointestinal tract. Peak plasma concentrations are reached in 2 hours; by 24 hours the serum concentrations are virtually zero. Approximately 80% of an oral or intravenous dose of 7 to 30 mg/kg may be recovered from the urine within 12 hours. Hydroxycarbamide crosses the blood-brain barrier. Hydroxycarbamide is well distributed throughout the body.

5.3 Preclinical safety data

Hydroxycarbamide is unequivocally genotoxic and a presumed transpecies carcinogen which implies a carcinogenic risk to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous

Lactose monohydrate

Magnesium stearate

Sodium phosphate

Gelatin capsules contain:

Erythrosine (E127)

Indigotine (E132)

Yellow iron oxide (E172)

Titanium dioxide (E171)

Sodium laurilsulfate (as processing aid)

Opacode S-1-277002

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Carton containing 100 capsules in blisters consisting of PVC/PCTFE/PVC and sealed with aluminium foil with PVC/PVDC backing.

6.6 Special precautions for disposal and other handling

Cytostatics must always be handled with care. Procedures for correct handling of cytostatics should be followed. 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. Pregnant personnel should not handle this medicinal product. Keep Hydrea out of the sight and reach of children and pets. People who are not taking Hydrea should not be exposed to the product. Always take precautions to prevent exposure, e.g. by wearing gloves and washing hands with soap

and water before and after each handling of such products. The contents of capsules should not be inhaled or allowed to come into contact with the skin or mucous membranes. Spilled powder must be immediately wiped up using a damp disposable tissue and discarded in a closed container, as should the empty capsules. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Arzneimittel GmbH
Ziegelhof 24
17489
Greifswald
Germany

8 MARKETING AUTHORISATION NUMBER

PA2239/021/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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