# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Hydrea 500 mg Hard Capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500 mg of Hydroxycarbamide.
Excipients with known effect: Contains Lactose Monohydrate 42.2 mg

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

*Adults*

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.

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.

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 $2.5x10^9$/L or the platelet count below $100x10^9$/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.

Severe gastric distress, such as nausea, vomiting, and anorexia, resulting from combined therapy may usually be controlled by interruption of Hydrea administration.

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.

*Continuous therapy*
Hydrea 20-30 mg/kg 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*

Hydrea 80 mg/kg 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.

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

*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.

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.

**4.3 Contraindications**

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

Marked leucopenia (<2.5WBCx$10^9$/L), thrombocytopenia (<100x$10^9$/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
Hydroxycarbamide should be used with caution in patients with renal dysfunction.

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 2.5x$10^9$/L or Platelet count to <100x$10^9$/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. 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 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. 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 hemolytic anemia in patients treated with HYDREA for myeloproliferative diseases have been reported (See Section 4.8 UNDESIRABLE EFFECTS). Patients who develop persistent anemia should have laboratory tests evaluated for hemolysis. In the setting of confirmed diagnosis of hemolytic anemia, 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.

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 polycythemia vera and thrombocythemia, secondary leukemia 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.

Lactose
This product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 hydroxyurea and treatment with corticosteroids appears to be associated with resolution of the pulmonary events (see section 4.8).

**4.5 Interaction with other medicinal products and other forms of interaction**

The myelosuppressive activity may be potentiated by previous or concomitant radiotherapy or cytotoxic therapy.

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/$mm^3$.

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).

**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.
Hydroxyurea 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**

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/$mm^3$ (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/$mm^3$) 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, muscloskeletal, 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 | MedDRA Term |
|---|---|---|
| Infections and Infestations | Rare | Gangrene |
| Neoplasms Benign and Malignant (including cysts and polyps) | Common | Skin cancer |
| Blood and Lymphatic System Disorders | Very common | Bone marrow failure, CD4 lymphocytes decreased, leukopenia, thrombocytopenia, platelet count decreased, anaemia |
| | Not Known | Hemolytic anemia |
| Metabolism and Nutrition Disorders | Very common | Anorexia |
| | Rare | Tumor 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 |
| | Unknown | 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 |
| Musculoskeletal and Connective Tissue Disorders | Unknown | Systemic lupus erythematosus |
| Skin and Subcutaneous Tissue Disorders | Very common<br><br>Not known<br><br>Very rare | Cutaneous vasculitis, dermatomyositis, alopecia, rash maculo-papular, rash papular, skin exfoliation, skin atrophy, skin ulcer, erythema, skin hyperpigmentation, nail disorder<br><br>Nail pigmentation<br><br>Systemic and cutaneous lupus erythematosus |
| Renal and Urinary Disorders | Very common | Dysuria, blood creatinine increased, blood urea increased, blood uric acid increased |
| General Disorders and Administration Site Conditions | Very common | Pyrexia, asthenia, chills, malaise |
| Reproductive system and breast disorders | Very common | azoospermia, oligospermia |

[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.

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
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971; Fax: +353 1 6762517.
Website: www.hpra.ie; E-mail: medsafety@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, 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**

People who are not taking Hydrea should not be exposed to it. To decrease the risk of exposure, wear disposable gloves when handling Hydrea. Anyone handling Hydrea should wash their hands before and after contact with the capsules. If the powder is spilled, it should be immediately wiped with a damp disposable towel and discarded in a closed container, such as a plastic bag, as should the empty capsules. Hydrea should be kept away from children and pets.

To minimise the risk of dermal exposure, always wear impervious gloves when handling capsules containing Hydrea. 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. 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**

Date of first authorisation: 01 April 1979

Date of last renewal: 01 April 2009

**10 DATE OF REVISION OF THE TEXT**

June 2023