1.3.1.1 Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

HYDREA 500 mg CAPSULES

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500 mg hydroxyurea.

Excipients with known effect: HYDREA contains sugar (42,2 mg lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

Size "0" gelatin capsule, green opaque cap and pink opaque body, CHP 500 is imprinted on both cap and body of capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HYDREA is intended for use in the treatment of chronic myeloid leukaemia and squamous cell carcinoma of the head and neck (excluding the lip).

4.2 Posology and method of administration

All HYDREA dosage regimens should be based on the patient's actual or ideal weight, whichever is less. Concurrent use of HYDREA with other myelosuppressive agents may require adjustments of dosages.

INSTRUCTIONS FOR HANDLING:

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.

Patients who take HYDREA by emptying the contents of the capsule into water should be reminded that this is a potent medicine that must be handled with care. Patients must be cautioned not to allow the powder to come in contact with the skin and mucous membranes, including avoidance of inhaling the powder when opening the capsules. People who are not taking HYDREA should not be exposed to it. To decrease the risk of exposure, wear disposable gloves when handling HYDREA or bottles containing HYDREA. Anyone handling HYDREA should wash their hands before and after contact with the bottle or capsules. If the powder is spilled, it should be immediately wiped up 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 bottles containing HYDREA. This includes all handling activities, activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

Procedures for proper handling and disposal of anticancer medicines should be considered.

Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

SOLID TUMORS

Intermittent Therapy

80 mg/kg administered orally as a single dose every third day.

Continuous Therapy

20 to 30 mg/kg administered orally as a single dose daily.

The intermittent dosage schedule offers the advantage of reduced toxicity (e.g. bone marrow depression). Patients on this dosage regimen have rarely required complete discontinuance of therapy because of toxicity.

Concomitant Therapy with Irradiation

(Carcinoma of the head and neck)

80 mg/kg administered orally as a single dose every third day.

Administration of HYDREA should begin at least seven days before initiation of irradiation and be continued during radiotherapy as well as indefinitely afterwards provided that the patient is kept under adequate observation and shows no unusual or severe reactions. Irradiation should be given at the maximum dose considered appropriate for the particular therapeutic situation; adjustment of irradiation dosage is not usually necessary when HYDREA is used concomitantly.

RESISTANT CHRONIC MYELOCYTIC LEUKAEMIA

Continuous therapy

20 to 30 mg/kg administered orally as a single dose daily.

An adequate trial period for determining the antineoplastic effectiveness of HYDREA is six weeks of therapy. When there is significant clinical response, therapy should be continued indefinitely. Therapy should be interrupted if the white blood cell count drops below 2500/mm^3 or the platelet count below 100 000/mm^3. In these cases, the counts should be rechecked after three days and therapy resumed when the counts rise above these trigger levels (WBC $\geq$ 2500/mm^3 or Pit $\geq$ 100 000/mm^3. If rapid rebound has not occurred during combined HYDREA and irradiation therapy, irradiation may also be interrupted. However, the need for postponement of irradiation has been rare; radiotherapy has usually been continued using the recommended dosage and technique. Anaemia, if it occurs, should be corrected without interrupting HYDREA therapy.

Renal Insufficiency

Since renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage in this population. Close monitoring of haematologic parameters is advised (see section 4.4).

Hepatic Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with impaired hepatic function. Close monitoring of haematologic parameters are advised.

Elderly

Elderly patients may require a lower dose regimen (see section 4.4).

NOTE: 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 (see section 4.2).

Procedures for proper handling and disposal of HYDREA should be adhered to.

DOSAGE CHART

BODY MASS (KG)	**INTERMITTENT THERAPY** 80 mg/kg every 3 days as single doses (capsules)	**CONTINUOUS THERAPY** 20 - 30 mg/kg daily as single daily doses (capsules)
10	1,5	0,5
15	2	1
20	3	1
30	5	2
40	6	2
50	8	3
60	10	3
70	11	4
80	13	4
90	14	5

100	16	6

4.3 Contraindications

HYDREA is contraindicated in:

- patients who have demonstrated a previous hypersensivity to hydroxyurea or any other component in HYDREA
- patients with bone marrow depression, i.e. leukopenia (< 2500 WBC/mm^3) or thrombocytopenia (< 100 000/mm^3), or severe anaemia.
- patients concomitantly using antiretroviral (ARV) medicines (see section 4.4).
- pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Myelosuppression:

Treatment with HYDREA should not be initiated if bone marrow function is depressed (see section 4.3). Bone marrow suppression may occur during treatment with HYDREA, and leukopenia is generally its first and most common manifestation. Thrombocytopenia and anaemia occur less often and are seldom seen without a preceding leukopenia.

However, the recovery from myelosuppression is rapid when therapy is interrupted. It should be borne in mind that 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).

Anaemia:

Severe anaemia must be corrected with whole blood replacement before initiating therapy with HYDREA.

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 B_{12} 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.

Radiation recall:

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

Macrocytosis:

Erythrocytic abnormalities: macrocytic anaemia, which is self-limiting, is often seen early in the course of HYDREA therapy. The morphologic change is not related to vitamin B12 or folic acid deficiency. The macrocytosis may mask the incidental development of folic acid deficiency, thus prophylactic administration of folic acid may be warranted. HYDREA may also delay plasma iron clearance and reduce the rate of iron utilisation by erythrocytes, but it does not appear to alter the erythrocyte survival time.

Renal impairment:

HYDREA should be used with caution in patients with marked renal dysfunction (see section 4.2).

Paediatric Use:

Safety and effectiveness in children have not been established.

Use in the elderly:

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

Secondary malignancies:

In patients receiving long-term therapy with HYDREA for myeloproliferative disorders such as polycythemia vera and thrombocythemia, secondary leukaemia has been reported. It is unknown whether this leukomogenic effect is secondary to HYDREA or associated with the patients' underlying disease.

Skin cancer has also been reported in patients receiving long-term HYDREA.

Use with radiation therapy and/or chemotherapy:

Because haematopoiesis may be compromised by extensive irradiation or by antineoplastic agents, it is recommended that HYDREA be administered cautiously to patients who have recently received extensive radiation therapy with other cytotoxic medicines.

Pain or discomfort from inflammation of the mucous membranes at the irradiated site (mucositis) is usually controlled by measures such as topical anaesthetics 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 be controlled by interruption of HYDREA administration. However, the additional interruption of irradiation therapy is necessary as well.

Use in HIV-infected patients:

Fatal and non-fatal pancreatitis has occurred in HIV-infected patients during therapy with HYDREA and didanosine with or without stavudine. Hepatotoxicity and hepatic failure resulting in death were reported during post marketing surveillance in HIV-infected patients treated with HYDREA and other antiretroviral medicines. Fatal hepatic events were reported most often in patients treated with the combination of HYDREA, didanosine and stavudine (see section 4.3).

Peripheral neuropathy, which may be severe, has been reported in HIV-infected patients receiving HYDREA in combination with antiretroviral medicines, including didanosine with or without stavudine (see section 4.3).

Vasculitic toxicities:

Cutaneous vasculitic toxicities including vasculitic ulcerations and gangrene have occurred in patients with myeloproliferate disorders during therapy with HYDREA. These vasculitic toxicities were reported also 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 with myeloproliferate disease, HYDREA should be discontinued if cutaneous vasculitic ulcerations develop and alternative cytoreductive agents should be initiated as indicated.

Patients should be advised to maintain adequate fluid intake.

Live vaccinations:

The use of live vaccines in patients taking HYDREA should be avoided during treatment and for at least six months after treatment has finished and individual specialist advice sought (see section 4.5). Concomitant use of HYDREA with a live virus vaccine may potentiate the replication of the virus and/or may increase the adverse reaction of the vaccine 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.

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

Lactose

HYDREA contains lactose. Patients with rare hereditary conditions of galactose intolerance, e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take HYDREA.

4.5 Interaction with other medicines and other forms of interaction

Since HYDREA may raise the serum uric acid level, dosage adjustment of uricosuric medication may be necessary. Vasculitic toxicities were reported in patients with a history of, or currently receiving, interferon therapy (see section 4.4). In vitro studies have shown a significant increase in cytarabine cytotoxic activity in HYDREA-treated cells. Whether this interaction will lead to synergistic toxicity in the clinical setting or the need to modify cytarabine doses has not been established.

Studies have shown that there is an analytical interference of hydroxyurea 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 HYDREA.

Concurrent use of HYDREA and other myelosuppressive agents or radiation therapy may increase the likelihood of bone marrow depression or other adverse events (see section 4.4).

Fatal and non-fatal pancreatitis has occurred in HIV-infected patients during therapy with HYDREA and didanosine, with or without stavudine. Fatal hepatic events were reported most often in patients treated with the combination of HYDREA, didanosine and stavudine (see section 4.3).

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

HYDREA is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy

HYDREA can cause foetal harm when administered to pregnant women and has been demonstrated to be a potent teratogen in a wide variety of animal models. There are no adequate and well-controlled studies in pregnant women.

Women of childbearing potential should avoid becoming pregnant while taking HYDREA.

They should continue with their contraception treatment for not less than 6 months after therapy with HYDREA has ended. Males on HYDREA who have partners who are women of childbearing potential should continue using reliable methods of contraception for at least 12 months after therapy with HYDREA has ended. They should not attempt to father children during this period.

When appropriate, patients should be counselled concerning the use of contraceptive measures during therapy. Medicines which affect DNA synthesis, such as HYDREA, may be mutagenic, and this should be considered before administering HYDREA to male or female patients who may still contemplate conception.

Breastfeeding

HYDREA is secreted in human milk. Women receiving HYDREA should not breastfeed their infants (see section 4.3).

Fertility

HYDREA is unequivocally genotoxic and a presumed transspecies carcinogen, which implies a carcinogenic risk to humans.

Men under therapy are advised to use effective contraceptive measures during and at least 1 year after therapy.

Male fertility may be compromised with the use of 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.

4.7 Effects on ability to drive and use machines

HYDREA may cause drowsiness and other neurologic effects (see section 4.8), that may affect a patient's ability to drive and use machines.

4.8 Undesirable effects

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 re-administration 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 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, decreased CD4 lymphocytes, leukopenia, thrombocytopenia, decreased platelet count, anaemia
Metabolism and nutrition disorders	Very common	Anorexia
	Rare	Tumor lysis syndrome
Psychiatric disorders	Common	Hallucination, disorientation
Nervous system disorders	Common	Convulsions, dizziness, peripheral neuropathy, somnolence, headache
Respiratory, thoracic and mediastinal disorders	Common	Pulmonary fibrosis, 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
Hepatobiliary disorders	Common	Hepatotoxicity[1], increased hepatic enzyme, cholestasis, hepatitis
Skin and subcutaneous tissue disorders	Very common	Cutaneous vasculitis, dermatomyositis, alopecia, maculopapular rash, skin exfoliation, skin atrophy, skin ulcer, erythema, skin hyperpigmentation, nail disorder. Systemic and cutaneous lupus erythematosus
	Not known	Nail pigmentation
Renal and urinary disorders	Very common	Dysuria, increased blood creatinine, increased blood urea, increased blood uric acid
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 have been reported in HIV-infected patients who received hydroxyurea in combination with antiretroviral medicines, in particular didanosine plus stavudine.

Combined HYDREA and Irradiation Therapy

Adverse reactions observed with combined HYDREA and irradiation therapy were similar to those reported with the use of HYDREA alone, primarily bone marrow depression (anaemia and leukopenia), 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 less frequently and usually in the presence of marked leukopenia. HYDREA may potentiate some adverse reactions usually seen with radiation alone, such as gastric distress and mucositis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects will be exacerbated and exaggerated (see section 4.8). Acute mucocutaneous toxicity has been reported in patients receiving HYDREA at a dosage several times the therapeutic dose. Soreness, violet erythema, oedema on palms and foot soles followed by scaling of hands and feet, severe generalised hyperpigmentation of skin, and stomatitis have also been observed. Treatment of overdosage should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytostatic agents.

The precise mechanism by which hydroxyurea produces its antineoplastic effects is not known. Various studies in tissue culture, rats, and humans support the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or protein.

Three mechanisms have been postulated for the potentiation of the therapeutic effect of irradiation by hydroxyurea on squamous cell (epidermoid) carcinomas of the head and neck.

In vitro studies utilizing Chinese hamster cells suggest that hydroxyurea (1) is lethal to normally radioresistant S-stage cells and (2) holds other cells of the cell cycle in the G1 or pre-DNA synthesis stage where they are most susceptible to the effects of irradiation.

The third mechanism of action has been theorized on the basis of *in vitro* studies of HeLa cells: it appears that hydroxyurea, by inhibition of DNA synthesis, hinders the normal repair process of cells damaged but not killed by irradiation, thereby decreasing their survival rate. There is no alteration of RNA and protein syntheses.

5.2 Pharmacokinetic properties

Absorption:

Hydroxyurea is readily absorbed after oral administration. Peak plasma levels are reached after 1-4 hours. There are no data on the effect of food on the absorption of hydroxyurea.

Distribution:

Hydroxyurea distributes rapidly and widely in the body with an estimated volume of distribution approximating total body water. Hydroxyurea concentrates in leukocytes and erythrocytes. Hydroxyurea crosses the blood-brain-barrier.

Elimination:

Elimination of hydroxyurea in humans is a non-linear process occurring through two pathways: hepatic metabolism and renal excretion. In patients with malignancies, renal elimination ranged from 25 - 55 % of the administered dose. The concentration in the serum at 24 hours is negligible when the usual dose is given as a single daily dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous

Lactose monohydrate

Magnesium stearate

Sodium phosphate

Gelatin capsule contain:

Opaque green cap:

Yellow iron oxide (E172)

Indigotine E132

Titanium dioxide (E171)

Gelatin

Opaque pink body:

Erythrosine BS E127

Titanium dioxide

Gelatin

Opacode S-1-277002

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C. Avoid excessive heat. Keep tightly closed.

(See section 4.2 INSTRUCTIONS FOR HANDLING.)

6.5 Nature and contents of container

Bottles of 100 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd*

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene

Pretoria, 0157

8. REGISTRATION NUMBER(S)

H2753 (Act 101 of 1965)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 March 2019

10. DATE OF REVISION OF THE TEXT

20 July 2020

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