AUSTRALIAN PRODUCT INFORMATION – HYDREA® (HYDROXYUREA)

1 NAME OF THE MEDICINE

Hydroxyurea.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

HYDREA (hydroxyurea) is an antineoplastic agent, available for oral use as capsules containing 500mg hydroxyurea.

List of excipients with known effect:

Each 500 mg capsule contains 42.2 mg of lactose.

3 PHARMACEUTICAL FORM

Capsules containing 500mg hydroxyurea; opaque aqua/opaque pink capsule shell, printed with "BMS 303".

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Significant tumour response to HYDREA has been demonstrated in, chronic myelocytic leukaemia (pretreatment phase and palliative care) and recurrent, metastatic, or inoperable carcinoma of the ovary.

4.2 DOSE AND METHOD OF ADMINISTRATION

Because of the rarity of melanoma, resistant chronic myelocytic leukaemia, carcinoma of the ovary, and carcinomas of the head and neck in children, dosage regimens have not been established.

All dosage should be based on the patient's actual or ideal weight, whichever is less. 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. Some inert material used as a vehicle in the capsule may not dissolve, and may float to the surface.

Elderly patients may require a lower dose regimen.

Patients who take the drug by emptying the contents of the capsule into water should be reminded that this is a potent medication 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 towel and disposed of in a closed container, such as a plastic bag, as should the empty capsules. The medication, particularly the open capsules, should be kept away from children and pets.

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

Solid Tumours

Intermittent Therapy - 80mg/kg administered orally as a *single dose* every *third* day.

Continuous Therapy - 20 to 30mg/kg administered orally as a *single dose* daily.

The intermittent dosage schedule offers the advantage of reduced toxicity since 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*) - 80mg/kg administered orally as a *single dose* every *third* day.

Administration of hydroxyurea should be begun at least seven days before initiation of irradiation and continued during radiotherapy as well as indefinitely afterwards provided that the patient may be kept under adequate observation and evidences 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 hydroxyurea is used concomitantly.

Resistant Chronic Myelocytic Leukaemia

Until the intermittent therapy regimen has been evaluated, CONTINUOUS therapy (20 to 30mg/kg administered orally as a *single dose daily*) is recommended.

An adequate trial period for determining the antineoplastic effectiveness of hydroxyurea is six weeks of therapy. When there is regression in tumour size or arrest in tumour growth, 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 significantly toward normal values. Since the haematopoietic rebound is prompt, it is usually necessary to omit only a few doses. If prompt rebound has not occurred during combination 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 with whole blood replacement, without interrupting hydroxyurea therapy. Because haematopoiesis may be compromised by extensive irradiation or by other antineoplastic agents, it is recommended that hydroxyurea be administered cautiously to patients who have recently received extensive radiation therapy or chemotherapy with other cytotoxic drugs.

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, hydroxyurea therapy may be temporarily interrupted; if it is extremely severe, irradiation therapy may, in addition, be temporarily postponed. However, it has rarely been necessary to terminate these therapies.

Severe gastric distress, such as nausea, vomiting, and anorexia, resulting from combined therapy may usually be controlled by temporary interruption of hydroxyurea administration; rarely has the additional interruption of irradiation been necessary.

Renal Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with impaired renal function. 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.

Hepatic Insufficiency

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

4.3 CONTRAINDICATIONS

Hydroxyurea is contraindicated in patients with marked bone marrow depression, i.e. leucopoenia (<2500WBC/mm^3) thrombocytopenia (< 100,000/mm^3), or severe anaemia.

A previous hypersensitivity to hydroxyurea or any other component of its formulation

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Concurrent use of hydroxyurea and other myelosuppressive agents or radiation therapy may increase the likelihood of bone marrow depression as other adverse events.

Treatment with hydroxyurea should not be initiated if bone marrow function is markedly depressed (see CONTRAINDICATIONS). Bone marrow suppression may occur, and leucopoenia is generally its first and most common manifestation. Thrombocytopenia and anaemia occur less often, and are seldom seen without a preceding leucopoenia. 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; hydroxyurea should be used cautiously in such patients.

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

Fatal and nonfatal pancreatitis have occurred in HIV-infected patients during therapy with hydroxyurea and didanosine, with or without stavudine. Hepatotoxicity and hepatic failure resulting in death have been reported during post-marketing surveillance in HIV-infected patients treated with hydroxyurea and other antiretroviral agents. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine, and stavudine. This combination should be avoided. Peripheral neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving hydroxyurea in combination with antiretroviral agents, including didanosine, with or without stavudine.

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

Erythrocytic abnormalities: megaloblastic erythropoiesis, which is self-limiting, is often seen early in the course of hydroxyurea therapy. The morphologic change resembles pernicious anaemia, but it 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. Hydroxyurea 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.

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

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

Therapy with hydroxyurea requires close supervision. 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. The determination of the haemoglobin level, total leucocyte counts, and platelet counts should be performed at least once a week throughout the course of hydroxyurea therapy. If the white blood cell count decreases to less than $2500/mm^3$, or the platelet count to less than $100{,}000/mm^3$, therapy should be interrupted until the values rise significantly toward normal levels. Anaemia, if it occurs, should be managed with whole blood replacement, without interrupting hydroxyurea therapy.

Since hydroxyurea may cause drowsiness and other neurologic effects alertness may be impaired in driving or in operating machinery.

Patients should be advised to maintain adequate fluid intake. Patients should consult with their physician or pharmacist regarding missed doses.

Hydroxyurea is not indicated for the treatment of HIV-infection; however if HIV-infected patients are treated with hydroxyurea, and in particular, in combination with didanosine and/or stavudine, close monitoring for signs and symptoms of pancreatitis and hepatotoxicity is recommended. Patients who develop signs and symptoms of pancreatitis or hepatotoxicity should permanently discontinue therapy with hydroxyurea. (See PRECAUTIONS above and ADVERSE EFFECTS sections).

Cutaneous vasculitic toxicities including vasculitic ulcerations and gangrene have occurred in patients with myeloproliferative disorders during therapy with hydroxyurea. 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, hydroxyurea should be discontinued if cutaneous vasculitic ulcerations develop and alternative cytoreductive agents should be initiated as indicted.

Use in hepatic Impairment

No information available.

Use in renal Impairment

Hydroxyurea should be used with caution in patients with marked renal dysfunction.

Use in the elderly

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

Paediatric use

Safety and efficacy have not been established in children.

Effects on laboratory tests

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 hydroxyurea. (See 4.5 Interactions with other medicines and other forms of interaction.)

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Concurrent use of hydroxyurea and other myelosuppressive agents or radiation therapy may increase the likelihood of bone marrow depression or other adverse events (See PRECAUTIONS).

Vaccinations

Concomitant use of HYDREA 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 HYDREA. Vaccination with a live vaccine in a patient taking HYDREA may result in severe infection. Patient's antibody response to vaccines may be decreased. The use of live vaccines should be avoided and individual specialist advice sought.

Other interactions

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 hydroxyurea. Since hydroxyurea may raise the serum uric acid level, dosage adjustment of uricosuric medication may be necessary.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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 the therapy.

Hydroxyurea may be genotoxic. Men under therapy are advised to use safe contraceptive measures during and at least 1 year after therapy.

Use in pregnancy

Pregnancy Category (Category D)

Drugs which affect DNA synthesis, such as hydroxyurea, may be potential mutagenic agents. The physician should carefully consider this possibility before administering this drug to male or female patients who may contemplate conception.

Hydroxyurea has been demonstrated to be a potent teratogenic agent in animals and can cause foetal harm when administered to a pregnant woman. Therefore, hydroxyurea should not be used in women who are or may become pregnant unless in the judgement of the physician the potential benefits outweigh the possible hazards. Women of childbearing potential should be advised to avoid becoming pregnant while taking hydroxyurea.

Use in lactation.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

ADVERSE EFFECTS

Adverse reactions have been primarily bone marrow depression (leucopoenia, anaemia, and occasionally thrombocytopenia), and less frequently gastrointestinal symptoms (stomatitis, anorexia, nausea, vomiting, diarrhoea, and constipation), and dermatological reactions such as maculopapular rash, facial erythema, peripheral erythema, hyperpigmentation, erythema, atrophy of skin and nails, nail pigmentation, skin ulceration, dermatomyositis-like skin changes, scaling and violet papules have been observed. Skin cancer has also been reported rarely. Dysuria and alopecia occur very rarely. Large doses may produce moderate drowsiness. Neurological disturbances have occurred extremely rarely and were limited to headache, dizziness, disorientation, hallucinations and convulsions. Hydroxyurea occasionally may cause temporary impairment of renal tubular function accompanied by elevations in serum uric acid, BUN, and creatinine levels. Abnormal BSP retention has been reported. Fever, chills, malaise, asthenia, azoospermia, oligospermia, cholestasis, hepatitis, tumour lysis syndrome, and elevation of hepatic enzymes have also been reported. Adverse reactions observed with combined hydroxyurea and irradiation therapy are similar to those reported with the use of hydroxyurea alone. These effects primarily include bone marrow depression (anaemia and leucopoenia) and gastric irritation. Almost all patients receiving an adequate course of combined hydroxyurea and irradiation therapy will demonstrate concurrent leucopoenia. Platelet depression (less than 100,000 cells/mm^3) has occurred rarely and only in the presence of marked leucopoenia. Gastric distress has also been reported with irradiation alone and in combination with hydroxyurea therapy.

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 hydroxyurea. Upon re-administration fever re-occurred within 24 hours.

It should be borne in mind that therapeutic doses of irradiation alone produce the same adverse reactions as hydroxyurea; combined therapy may cause an increase in the incidence and severity of these side effects.

Although inflammation of the mucous membranes at the irradiated site (mucositis) is attributed to irradiation alone, some investigators believe that the more severe cases are due to combination therapy.

The association of hydroxyurea with the development of acute pulmonary reactions consisting of diffuse pulmonary infiltrates fibrosis, fever and dyspnoea has been rarely reported.

Fatal and nonfatal pancreatitis and hepatotoxicity, and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxyurea in combination with anti-retroviral agents, in particular, didanosine plus stavudine. Patients treated with hydroxyurea in combination with didanosine, stavudine, and indinavir showed a median decline in CD4 cells of approximately 100/mm^3. (See PRECAUTIONS)

Cutaneous vasculitic toxicities including vascultic ulcerations and gangrene have occurred in patients with myeloproliferative disorders during therapy with hydroxyurea. These vasculitic toxicities were reported most often in patients with a history of or currently receiving interferon therapy (See PRECAUTIONS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Acute mucocutaneous toxicity has been reported in patients receiving hydroxyurea at dosages several times the therapeutic dose. Soreness, violet erythema, edema on palms and foot soles followed by scaling of hands and feet, severe generalized hyperpigmentation of skin, and stomatitis have also been observed.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The precise mechanism by which hydroxyurea produces its cytotoxic effects cannot, at present, be described. However, the reports of various studies in tissue culture, rats and man lend support to the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis without interfering with the synthesis of ribonucleic acid or of protein. This hypothesis explains why, under certain conditions, hydroxyurea may induce teratogenic effects.

Three mechanisms of action have been postulated for the increased effectiveness of concomitant use of hydroxyurea therapy with irradiation on squamous cell (epidermoid) carcinomas of the head and neck. *In vitro* studies utilising 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 theorised 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; RNA and protein synthesis have shown no alteration.

5.2 PHARMACOKINETIC PROPERTIES

After oral administration in man, hydroxyurea is readily absorbed from the gastrointestinal tract. The drug reaches peak serum concentrations within 2 hours; by 24 hours the concentration in the serum is essentially zero. Approximately 80% of an oral or intravenous dose of 7 to 30 mg/kg may be recovered in the urine within 12 hours.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

In patients receiving long-term hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported; it is unknown whether this leukemogenic effect is secondary to hydroxyurea or the patients underlying disease. Skin cancer has also been reported in patients receiving long-term hydroxyurea. Patients should be advised to protect skin from sun exposure, conduct self-inspection of the skin and be screened from secondary malignancies during routine follow-up visits.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The capsules contain the inactive ingredients: citric acid, gelatin, lactose, magnesium stearate, dibasic sodium phosphate, titanium dioxide, sodium lauryl sulfate and capsule colourants (erythrosine, indigo carmine and iron oxide yellow).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Avoid excessive heat. Keep bottle tightly closed.

6.5 NATURE AND CONTENTS OF CONTAINER

HYDREA (hydroxurea) in bottles containing 100 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

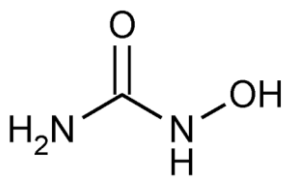
Guidelines for proper handling and disposal of anticancer drugs

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

To minimize the risk of dermal exposure, always wear impervious gloves when handling bottles containing HYDREA capsules. 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.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Empirical Formula: $CH_4N_2O_2$

Molecular Weight: 76.05 g/mole

Hydroxyurea is an essentially tasteless, white to off-white crystalline powder. It is hygroscopic and freely soluble in water, but practically insoluble in alcohol.

CAS number

127-07-1.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8 SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
4 Nexus Court, Mulgrave,
Victoria 3170, Australia.
Toll free number: 1800 067 567
Email: MedInfo.Australia@bms.com

9 DATE OF FIRST APPROVAL (ARTG ENTRY)

18 January 1994.

10 DATE OF REVISION OF THE TEXT

6 January 2020..

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Update to the SPC-style format
4.1 Therapeutic indications	Amendment to indication wording: "Significant tumour response to HYDREA has been demonstrated in chronic myelocytic leukaemia (pretreatment phase and palliative care) and recurrent, metastatic, or inoperable carcinoma of the ovary.

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