

Data Sheet

Name of Medicine

Hydrea

Hydroxyurea (hydroxycarbamide)

Presentation

Capsule: 500mg; opaque green and pink marked BMS 303, size 0 capsule shell.

Inactive ingredients include: citric acid, lactose, magnesium stearate, sodium phosphate and capsule colorants.

Uses

Actions

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 radio-resistant 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.

Pharmacokinetics

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

Hydroxyurea crosses the blood-brain barrier.

Indications

Significant tumour response to **Hydrea (hydroxyurea)** has been demonstrated in melanoma, resistant chronic myelocytic leukaemia, and recurrent metastatic or inoperable carcinoma of the ovary. **Hydrea** used concomitantly with irradiation therapy is intended for use in the local control of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip, and carcinoma of the cervix.

Dosage And 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.

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

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 on the surface.

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 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.

Solid Tumours :

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 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)

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

Administration of Hydrea (**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 Hydrea is used concomitantly.

Resistant Chronic Myelocytic Leukaemia: Continuous therapy:

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

An adequate trial period for determining the antineoplastic effectiveness of Hydrea 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/mm³, or the platelet count drops below 100,000/mm³. 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 combined **hydroxyurea** 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 Hydrea 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) it 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 dosage 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 Hydrea (**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.

Contraindications

Hydrea is contraindicated in patients who have demonstrated a previous hypersensitivity to **hydroxyurea** or any other component of its formulation.

Hydroxyurea is contraindicated in patients with marked bone marrow depression, i.e. leukopenia (< 2500 WBC/mm³) or thrombocytopenia ($< 100,000$ /mm³), or severe anaemia.

Warnings And Precautions

Warnings

Treatment with **hydroxyurea** should not be initiated if bone marrow function is markedly depressed (see Contraindications). Bone marrow suppression may occur, 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 the 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.

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

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

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

Fatal and nonfatal pancreatitis have occurred in HIV-infected patients during therapy with Hydrea V2.0

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.

Erythrocytic Abnormalities

Megaloblastic erythropoiesis, which is self-limiting is often seen early in the course of **hydroxyurea** therapy. The morphological 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; thus, prophylactic administration of folic acid may be warranted. **Hydroxyurea** 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.

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

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.

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 indicated.

Use in pregnancy

Hydroxyurea can cause fetal harm when administered to a pregnant woman and has been demonstrated to be a potent teratogenic agent in animals. Malformations have been observed in the offspring of rabbits and rats given doses equivalent to one-third to twice the maximum human dose, respectively. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while on **hydroxyurea** therapy, the patient should be apprised of the potential hazard of the fetus. 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**, breast feeding is not recommended during **hydroxyurea** therapy.

Hydrea V2.0

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 **hydroxyurea**, and may require a lower dose regimen.

Precautions

When appropriate, patients should be counselled concerning the use of contraceptive measures during therapy.

Concurrent use of **hydroxyurea** and other myelosuppressive agents or radiation therapy may increase the level of bone marrow depression or other adverse reactions (see Warnings and **Adverse Effects**).

Patients should be informed to maintain adequate fluid intake and to consult the physician regarding missed doses.

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 leukocyte 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 $2500/\text{mm}^3$, or the platelet count to less than $100\,000/\text{mm}^3$, 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.

Animal Pharmacology And Toxicology

The oral LD_{50} of **hydroxyurea** is 7330 mg/kg in mice and 5780 mg/kg in rats, given as a single doses.

In subacute and chronic toxicity studies in the rat, the most consistent pathological findings were an apparent dose-related mild to moderate bone marrow hypoplasia as well as pulmonary congestion and mottling of the lungs. At the highest dosage levels (1260 mg/kg/day for 37 days then 2520 mg/kg/day for 40 days), testicular atrophy with absence of spermatogenesis occurred. In several animals hepatic cell damage with fatty metamorphosis was noted. In the dog, mild to marked bone marrow depression was a consistent finding except at the lower dosage levels. Additionally, at the higher dose levels (140 to 420mg or 140 to 1260 mg/kg/week given 3 or 7 days weekly for 12 weeks), growth retardation, slightly increased blood glucose values, and haemosiderosis of the liver or spleen were found, reversible spermatogenic arrest was noted. In the higher, often lethal, doses (400 to 800 mg/kg/day for 7 to 15 days), haemorrhage and congestion were found in the lungs, brain, and urinary tract. Cardiovascular effects (change in

heart rate, blood pressure, orthostatic hypotension, EKG changes) and haematological changes (slight haemolysis, slight methemoglobinemia) were observed in some species of laboratory animals at doses exceeding clinical levels.

Carcinogenesis, Mutagenesis, Impairment Of Fertility

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

Adverse Effects

Haematological

Adverse reactions have been primarily bone marrow depression (leukopenia, anaemia, and occasionally thrombocytopenia). (See Warnings)

Gastrointestinal

Adverse gastrointestinal symptoms include stomatitis, anorexia, nausea, vomiting, diarrhoea, and constipation.

Dermatological

Dermatologic reactions include maculopapular rash, facial erythema, and peripheral erythema, skin ulceration, dermatomyositis-like skin rashes. Alopecia occurs rarely. Hyperpigmentation, erythema, atrophy of skin and nails, scaling, violet papules, and alopecia have been observed in some patients after several years of long-term daily maintenance therapy with **hydroxyurea**. Skin cancer has also been reported rarely.

Neurological

Large doses may produce moderate drowsiness. Neurological disturbances have occurred rarely and were limited to headache, dizziness, disorientation, hallucinations, and convulsions.

Renal

Hydroxyurea occasionally may cause temporary impairment of renal tubular function accompanied by elevations in serum uric acid, BUN, and creatinine levels. Dysuria occurs rarely.

Other

Fever, chills, malaise, asthenia, and elevation of hepatic enzymes have also been reported. The association of **hydroxyurea** with the development of acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fibrosis, pulmonary oedema, fever, and dyspnoea has been rarely reported.

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 (See **Warnings**)

Fatal and nonfatal 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. Patients treated with **hydroxyurea** in combination with didanosine, stavudine, and indinavir showed a median decline in CD4 cells of approximately 100/mm³ (See **Warnings and Precautions**).

Combined Hydroxyurea And Irradiation Therapy

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 leukopenia), and gastric irritation. Almost all patients receiving an adequate course of combined **hydroxyurea** and irradiation therapy will demonstrate concurrent leukopenia. Decreased platelet counts (<100,000/mm³) have occurred rarely and only in the presence of marked leukopenia. Gastric distress has also been reported with irradiation alone and in combination with **hydroxyurea** therapy.

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.

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 **Warnings and Precautions** and **Adverse Events**).

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

In vitro studies have shown a significant increase in cytarabine activity in **hydroxyurea**-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 **hydroxyurea**. Since **hydroxyurea** may raise the serum uric acid level, dosage adjustment of uricosuric medication may be necessary.

Overdosage

Acute mucocutaneous toxicity has been reported in patients receiving **hydroxyurea** at a dosage several fold in excess of the usual recommended dosage. Soreness, violet erythema, edema on palms and foot soles followed by scaling of hands and feet, intense generalised hyperpigmentation of skin, and severe acute stomatitis were observed.

In the case of overdosage implement immediate gastric lavage, followed by supportive cardiorespiratory therapy. Long term monitoring of the haemopoietic system is necessary.

Pharmaceutical Precautions

Store below 30 °C; avoid excessive heat; keep bottle tightly closed. Dispense in air-tight containers.

Procedures for proper handling and disposal of anticancer drugs 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.

Guidelines for proper handling and disposal of anticancer drugs

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.

Medicine Classifications

Prescription Medicine.

Package Quantities

Capsule, 500mg, 100s.

Name And Address

Bristol-Myers Squibb (NZ) Ltd
Simpson Grierson
88 Shortland Street
Auckland
New Zealand

Date Of Preparation

10 August 2011