BRISTOL-MYERS SQUIBB
ONCOLOGY

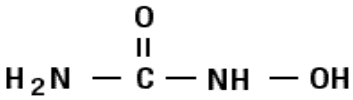
**Rx only**

# HYDREA®
## (hydroxyurea capsules, USP)

## DESCRIPTION

HYDREA® (hydroxyurea capsules, USP) is an antineoplastic agent, available for oral use as capsules providing 500 mg hydroxyurea. Inactive ingredients: citric acid, colorants (D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red 40 and D&C Red 28), gelatin, lactose, magnesium stearate, sodium phosphate, and titanium dioxide.

Hydroxyurea occurs as an essentially tasteless, white crystalline powder. Its structural formula is:



## CLINICAL PHARMACOLOGY

### Mechanism of Action

The precise mechanism by which hydroxyurea produces its antineoplastic effects cannot, at present, be described. However, the reports of various studies in tissue culture in rats and humans lend support to 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 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 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; RNA and protein syntheses have shown no alteration.

# Pharmacokinetics

## Absorption

Hydroxyurea is readily absorbed after oral administration. Peak plasma levels are reached in 1 to 4 hours after an oral dose. With increasing doses, disproportionately greater mean peak plasma concentrations and AUCs are observed.

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.

Plasma to ascites fluid ratios range from 2:1 to 7.5:1. Hydroxyurea concentrates in leukocytes and erythrocytes.

## Metabolism

Up to 50% of an oral dose undergoes conversion through metabolic pathways that are not fully characterized. In one minor pathway, hydroxyurea may be degraded by urease found in intestinal bacteria. Acetohydroxamic acid was found in the serum of three leukemic patients receiving hydroxyurea and may be formed from hydroxylamine resulting from action of urease on hydroxyurea.

## Excretion

Excretion of hydroxyurea in humans is a nonlinear process occurring through two pathways. One is saturable, probably hepatic metabolism; the other is first-order renal excretion.

# Special Populations

## Geriatric, Gender, Race

No information is available regarding pharmacokinetic differences due to age, gender or race.

## Pediatric

No pharmacokinetic data are available in pediatric patients treated with hydroxyurea.

## Renal Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with renal impairment. As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of hydroxyurea in patients with renal impairment. Close monitoring of hematologic parameters is advised in these patients.

### Hepatic Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

### Drug Interactions

There are no data on concomitant use of hydroxyurea with other drugs in humans.

## 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 dose.

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 420 mg or 140 to 1260 mg/kg/week given 3 or 7 days weekly for 12 weeks), growth retardation, slightly increased blood glucose values, and hemosiderosis of the liver or spleen were found; reversible spermatogenic arrest was noted. In the monkey, bone marrow depression, lymphoid atrophy of the spleen, and degenerative changes in the epithelium of the small and large intestines were found. At the higher, often lethal, doses (400 to 800 mg/kg/day for 7 to 15 days), hemorrhage and congestion were found in the lungs, brain, and urinary tract. Cardiovascular effects (changes in heart rate, blood pressure, orthostatic hypotension, EKG changes) and hematological changes (slight hemolysis, slight methemoglobinemia) were observed in some species of laboratory animals at doses exceeding clinical levels.

## INDICATIONS AND USAGE

Significant tumor response to HYDREA has been demonstrated in melanoma, resistant chronic myelocytic leukemia, and recurrent, metastatic, or inoperable carcinoma of the ovary.

Hydroxyurea 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.

## CONTRAINDICATIONS

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

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

## 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 anemia 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; hydroxyurea should be used cautiously in such patients.

Patients who have received irradiation therapy in the past may have an exacerbation of postirradiation 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. 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 anemia must be corrected 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 anemia, but is not related to vitamin $B_{12}$ or folic acid deficiency. Hydroxyurea may also delay plasma iron clearance and reduce the rate of iron utilization 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.

Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen (see **PRECAUTIONS**: **Geriatric Use**).

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 associated with the patient's underlying disease.

## Carcinogenesis and Mutagenesis

Hydroxyurea is genotoxic in a wide range of test systems and is thus presumed to be a human carcinogen. 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 is associated with the patient's underlying disease. Skin cancer has also been reported in patients receiving long-term hydroxyurea.

Conventional long-term studies to evaluate the carcinogenic potential of hydroxyurea have not been performed. However, intraperitoneal administration of 125-250 mg/kg hydroxyurea (about 0.6-1.2 times the maximum recommended human oral daily dose on a $mg/m^2$ basis) thrice weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to control. Hydroxyurea is mutagenic *in vitro* to bacteria, fungi, protozoa, and mammalian cells. Hydroxyurea is clastogenic *in vitro* (hamster cells, human lymphoblasts) and *in vivo* (SCE assay in rodents, mouse micronucleus assay). Hydroxyurea causes the transformation of rodent embryo cells to a tumorigenic phenotype.

## Pregnancy

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.

HYDREA can cause fetal harm when administered to a pregnant woman. Hydroxyurea has been demonstrated to be a potent teratogen in a wide variety of animal models, including mice, hamsters, cats, miniature swine, dogs and monkeys at doses within 1-fold of the human dose given on a $mg/m^2$ basis. Hydroxyurea is embryotoxic and causes fetal malformations (partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae) at 180 mg/kg/day (about 0.8 times the maximum recommended human daily dose on a $mg/m^2$ basis) in rats and at 30 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a $mg/m^2$ basis) in rabbits. Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. Hydroxyurea crosses the placenta. Single doses of ≥375 mg/kg (about 1.7 times the maximum recommended human daily dose on a $mg/m^2$ basis) to rats caused growth retardation and impaired learning ability. 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 taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

## PRECAUTIONS

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 hemoglobin 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/$mm^3$, or the platelet count to less than 100,000/$mm^3$, therapy should be interrupted until the values rise significantly toward normal levels. Severe anemia, if it occurs, should be managed without interrupting hydroxyurea therapy.

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 **WARNINGS** and **ADVERSE REACTIONS**.)

### Carcinogenesis, Mutagenesis, Impairment of Fertility

See **WARNINGS** for Carcinogenesis and Mutagenesis information.

Impairment of Fertility: Hydroxyurea administered to male rats at 60 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/$m^2$ basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

### Pregnancy

Pregnancy Category D. (See **WARNINGS**.)

### Nursing Mothers

Hydroxyurea is excreted in human milk.

Because of the potential for serious adverse reactions with 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.

### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

## Geriatric Use

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

This drug is known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function (see **DOSAGE AND ADMINISTRATION**: **Renal Insufficiency**).

## Drug Interactions

Prospective studies on the potential for hydroxyurea to interact with other drugs have not been performed.

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 **ADVERSE REACTIONS**.)

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

## Information for Patients

HYDREA is a medication that must be handled with care. People who are not taking HYDREA should not be exposed to it. If the powder from the capsule is spilled, it should be wiped up immediately with a damp disposable towel and discarded in a closed container, such as a plastic bag. The medication should be kept away from children and pets.

# ADVERSE REACTIONS

Adverse reactions have been primarily bone marrow depression (leukopenia, anemia, and occasionally thrombocytopenia), and less frequently gastrointestinal symptoms (stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation), and dermatological reactions such as maculopapular rash, skin ulceration, dermatomyositis - like skin changes, peripheral and facial erythema. Hyperpigmentation, atrophy of skin and nails, scaling and violet papules have been observed in some patients after several years of long-term daily maintenance therapy with HYDREA. Skin cancer has been reported. 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. HYDREA (hydroxyurea capsules, USP) 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, edema, asthenia, 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 or radiation treatment alone. These effects primarily include bone marrow depression (anemia and leukopenia), gastric irritation, and mucositis. Almost all patients receiving an adequate course of combined hydroxyurea and irradiation therapy will demonstrate concurrent leukopenia. Platelet depression (<100,000 cells/$mm^3$) has occurred rarely and only in the presence of marked leukopenia. HYDREA may potentiate some adverse reactions usually seen with irradiation alone, such as gastric distress and mucositis.

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

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 in Study ACTG 5025 showed a median decline in CD4 cells of approximately 100/$mm^3$. (See **WARNINGS** and **PRECAUTIONS**.)

## OVERDOSAGE

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

## DOSAGE AND ADMINISTRATION

Procedures for proper handling and disposal of antineoplastic drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Because of the rarity of melanoma, resistant chronic myelocytic leukemia, carcinoma of the ovary, and carcinomas of the head and neck in pediatric patients, 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 HYDREA with other myelosuppressive agents may require adjustment of dosages.

## 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*

### Concomitant Therapy with Irradiation

*Carcinoma of the head and neck*—80 mg/kg administered orally as a *single dose* every *third* day

Administration of hydroxyurea should begin 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.

## Resistant Chronic Myelocytic Leukemia

Until the intermittent therapy regimen has been evaluated, 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 hydroxyurea is six weeks of therapy. When there is regression in tumor size or arrest in tumor 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 re-evaluated after three days, and therapy resumed when the counts return to acceptable levels. Since the hematopoietic rebound is prompt, it is usually necessary to omit only a few doses. If prompt 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. Severe anemia, if it occurs, should be corrected without interrupting hydroxyurea therapy. Because hematopoiesis 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 anesthetics 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 hydroxyurea administration.

## Renal Insufficiency

There are no data that support specific guidance for dosage adjustments in patients with renal impairment. As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of HYDREA in patients with renal impairment. Close monitoring of hematologic parameters is advised in these patients.

## Hepatic Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

# HOW SUPPLIED

HYDREA® (hydroxyurea capsules, USP)

**500 mg capsules** in bottles of 100 (NDC 0003-0830-50).

Capsule identification number: 830. The cap is opaque green and the body is opaque pink. They are imprinted on both sections in black ink with “HYDREA” and “830”.

## Storage

Store at 25º C (77º F); excursions permitted to 15°-30º C (59°-86º F) [see USP Controlled Room Temperature]. Keep tightly closed.

# REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. *NIH Publications* No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.

2. AMA Council Report: Guidelines for Handling Parenteral Antineoplastics. *JAMA* 1985; 253 (11): 1590-1592.

3. *National Study Commission on Cytotoxic Exposure*—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, *Massachusetts College of Pharmacy and Allied Health Sciences*, 179 Longwood Avenue, Boston, MA 02115.

4. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia* 1983; 1:426-428.

5. Jones RB, *et al*: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center, *CA- A Cancer Journal for Clinicians* 1983; (Sept./Oct.) 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.

7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA WORK PRACTICE GUIDELINES). *Am J Health-Syst Pharm* 1996; 53:1669-1685.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