HYDRINE Capsule

Hydroxyurea 500 mg

COMPOSITION
Each capsule contains
Hydroxyurea ..... 500 mg

DESCRIPTION
Each hard capsule, with pink-colored cap and green-colored body, is filled with white to off-white powder.

PHARMACODYNAMICS
Hydroxyurea is an orally active antineoplastic agent. Although the mechanism of action has not yet been clearly defined, hydroxyurea appears to act by interfering with synthesis of DNA.

PHARMACOKINETICS
After oral administration hydroxyurea is readily absorbed from the gastrointestinal tract. Peak plasma concentrations are reached in 2 hours; by 24 hours the serum concentrations are virtually zero. Approximately 80% of an oral or intravenous dose of 7 to 30 mg/kg may be recovered from the urine within 12 hours. Hydroxyurea crosses the blood-brain barrier. Hydroxyurea is well distributed throughout the body.

INDICATIONS
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.

DOSAGE & ADMINISTRATIONS
Because of the rarity of melanoma, resistant chronic myelocytic leukemia, 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.

Concomitant Therapy
Concurrent use of HYDRINE with other myelosuppresive agents may require adjustments of dosage.

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 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 hydroxyurea should be begun at least seven days before initiation of irradiation and continued during radiotherapy and continue indefinitely afterwards provided 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 or irradiation dosage is not usually necessary when hydroxyurea is used concomitantly.

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. 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/mm3 or the platelet count 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 hematopoietic rebound is prompt, it is usually necessary to omit only a few doses. If prompt rebound has not occurred during combined Hydrea (Hydroxyurea Capsules USP) 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. Anemia, if it occurs, should be corrected with whole blood replacement, 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; rarely has the additional interruption of irradiation been necessary.

Renal Impairment
Since renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of HYDRINE in this population (See WARNINGS). Close monitoring of hematologic parameters is advised.

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

ROUTE OF ADMINISTRATION : Oral
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 float on the surface.

CONTRAINDICATIONS
Patients with marked bone marrow depression, i.e., leukopenia (< 2500 WBC/mm^3) or thrombocytopenia ($< 100{,}000/mm^3$)
Patients with severe anemia
Patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation.

WARNINGS AND PRECAUTIONS
Treatment with hydroxyurea should not be initiated if bone marrow function is markedly depressed. (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.)
It should be borne in mind that bone marrow depression is more likely in patients who have previously received radiotherapy of 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 postirradiationerythema.
Severe anemia must be corrected with whole blood replacement before initiating therapy with hydroxyurea.
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.
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 hydroxyurea and treatment with corticosteroids appears to be associated with resolution of the pulmonary events.

GENERAL PRECAUTIONS
1) 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. Anemia, if it occurs, should be managed with whole blood replacement, without interrupting hydroxyurea therapy.
2) 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 or mucous membranes.
3) 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.
4) Erythrocytic abnormalities: Megaloblastic erythropoiesis which is self-limiting, is often seen early in the course of hydroxyurea therapy. The morphologic change resembles that seen in pernicious anema, but is not related to vitamin B12 or folic acid deficiency. The marcrocytosis 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 utilization by erythrocytes, but is does not appear to alter the red blood cell survival time. Patients who have received irradiation therapy in the past may have an exacerbation of postirradiation erythema when hydroxyurea is given.
5) Sickle cell anemia: Patient with sickle cell anemia being treated with Hydroxyurea must be monitored closely for evidence for worsening anemia.
6) Secondary leukemia: In patients receiving long-term therapy with hydroxyurea for myeloproliferative disorders, secondary leukemia has been reported.

PEDIATRIC USE
Because of the rarity of carcinomas of the head and neck in children, dosage regimens have not been established. Also, safety and effectiveness in children have not been established.

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

ADVERSE REACTIONS
Psychoneural system: Rarely, headache, dizziness, disorientation, hallucinations, and convulsions may be caused.
Gastrointestinal: Stomatitis, inappetence, nausea, vomiting, diarrhea, and constipation may occur.
Hematologic: Primarily, bone marrow depression (leukopenia, anemia, thrombocytopenia) may occur. Megaloblastic erythropoiesis, which is self-limiting, is often seen early in the course of hydroxyurea therapy.
Urogenital system: Dysuria occur very rarely. Hydroxyurea occasionally may cause

temporary impairment of renal tubular function accompanied by elevations in serum uric acid, BUN, and creatinine levels.
Central Nervous System: At the higher dose, general lethargy state may be caused, and flush, chill, malaise have been reported.
Dermatologic: Occasionally, maculopapular rash, facial erythema may occur.
Hepatic: Abnormal BSP retention, elevation of hepatic enzymes have been reported.
Other: Very rarely, alopecia may be caused.
Adverse reactions observed with combined hydroxyurea and irradiation therapy were similar to those reported with the use of hydroxyurea alone, primarily bone marrow depression (leucopenia and anemia) and gastric irritation
Respiratory, Thoracic, and Mediastinal Disorders: Interstitial lung disease (unknown frequency)

DRUG INTERACTIONS
The myelosuppressieve activity may be potentiated by previous or concomitant radiotherapy or cytotoxic therapy.
Since hydroxyurea may raise the concentration or blood uric acid, dosage adjustment of antigout agents may be necessary to control hyperuricemia and gout. Allopurinol may be preferred to prevent or reverse hydroxyurea induced hyperuricemia because of risk of uric acid nepropathy with uricosuric antigout agents.
Leukopenia and/or thrombocytopenia effects of hydroxyurea may be increased with concurrent or recent therapy if “blood dyscrasia-causing medications” cause the same effects. Dosage adjustment of hydroxyurea, if necessary, should be based on blood counts.
Concurrent use with a live virus vaccine may potentiate the replication of the vaccine virus, may increase the adverse effects of the vaccine virus, and/or may decrease the patient’s antibody response to the vaccine.

USE IN PREGNANCY AND NURSING MOTHERS
Use in Pregnancy: Drugs which affect DNA synthesis, such as hydroxyurea, may be potent mutagenic agents. The physician should carefully consider this possibility before administering this drug to male or female patients who may contemplate conception. Hydroxyurea is a known teratogenic agent in animals.
Therefore, hydroxyurea should not be used in women who are or may become pregnant unless in the judment of the physician the potential benefits outweigh the possible hazards.
Nursing Mothers: Hydroxyurea is excreted in human breast milk. Because of the potential for serious adverse reactions with hydroxyurea, a decision should be made whether to discontinue nursing or to discontinue Hydroxyurea, taking into account the importance of the drug to the mother.

OVERDOSE
Acute mucocutaneous toxicity has been reported in patients receiving hydroxyurea at a dosage several times greater than that recommended. Soreness, violet erythema, oedema on palms and foot soles followed by scaling of hands and feet, intense generalised hyperpigmentation of skin, and severe acute stomatitis were observed.
Immediate treatment consists of gastric lavage, followed by supportive therapy for the cardiorespiratory systems if required. In the long term, careful monitoring of the haemopoietic system is essential and, if necessary, blood should be transfused.

INSTRUCTION FOR USE
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 hydroxyurea should not be exposed to it. To decrease the risk of exposure, wear disposable gloves when handling hydroxyurea or bottles containing hydroxyurea. Anyone handling hydroxyurea 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, as should the empty capsules. The medication, particularly the open capsules, should be kept away from children and pets.

To minimize the risk of dermal exposure, always wear impervious gloves when handling (blisters/bottles) containing hydroxyurea 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Hydroxyurea may cause drowsiness. Patients receiving it should not drive or operate machinery unless it has been shown not to affect physical or mental ability.

STORAGE
Preserve in well-closed containers, protected from light and moisture.
Store at room temperature not exceeding 30°C.

PACKAGE
10 Capsules/Blister x 10 Blisters/Box

Manufactured by:
KOREA UNITED PHARM INC.
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