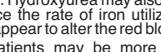
HYUTIZ 500
Hydoxyurea Capsules BP 500 mg

Rx only

COMPOSITION

HYUTIZ 500

Hydoxyurea Capsules BP 500 mg
Each Capsule Contains
Hydroxyurea BP 500 mg
Excipients q.s.



Colour: Approved colours used in capsule shell

DESCRIPTION

HYUTIZ is an antimetabolite available for oral use as capsules containing 500 mg hydroxyurea

HYUTIZ is a white to off-white crystalline powder. It is hygroscopic and freely soluble in water,but practically insoluble in alcohol.The empirical formula is $CH_4N_2O_2$ and it has a molecular weight of 76.05

CLINICAL PHARMACOLOGY

The precise mechanism by which hydroxyurea produces its anti neoplastic 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 therapy with irradiation on HYUTIZ squamous cell (epidermoid) carcinomas of the head and neck. In vitro studies utilizing 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 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.

INDICATIONS AND USAGE

HYUTIZ is indicated for the treatment of:

- Resistant chronic myeloid leukemia.
- Locally advanced squamous cell carcinomas of the head and neck (excluding the lip) in combination with chemoradiation.

CONTRAINDICATIONS

HYUTIZ is contraindicated in patients with marked bone marrow depression, ie, leukopenia (<2500 WBC) or thrombocytopenia (<100,000), or severe anemia. HYUTIZ is contraindicated in patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation.

WARNINGS

Hydroxyurea causes severe myelosuppression. Treatment with HYUTIZ 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. Bone marrow depression is more likely in patients who have previously received radiotherapy or cytotoxic cancer chemotherapeutic agents; use HYUTIZ cautiously in such patients.

Patients who have received irradiation therapy in the past may have an exacerbation of post irradiation erythema. In HIV-infected patients during therapy with and didanosine, with or without stavudine, fatal and nonfatal pancreatitis have occurred.

In HIV-infected patients during therapy with HYUTIZ and didanosine, with or without stavudine, fatal and nonfatal pancreatitis have occurred. Hepatotoxicity and hepatic failure resulting in death have been reported during postmarketing 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 anemia must be corrected before initiating therapy with hydroxyurea.

Erythrocytic abnormalities are megaloblastic erythropoiesis, which is self-limiting, is often seen early in the course of HYUTIZ therapy. The morphologic change resembles pernicious anemia, but is not related to vitamin B12 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.

Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen.In patients receiving long-term hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemiahas been reported. It is unknown whether this leukemogenic effect is secondary to HYUTIZ or associated with the patient's underlying disease.

Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders during therapy with HYUTIZ. 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.

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, or the platelet count to less than 100,000/mm, therapy should be interrupted until the values rise significantly toward normal levels. Severe anemia,must be corrected with whole blood replacement if it occurs, should be managed without interrupting hydroxyurea therapy.

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

HYUTIZ 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 ofpancreatitis and hepatotoxicity is recommended.

Patients who develop signs and symptoms of pancreatitis or hepatotoxicity should permanently discontinue therapy with hydroxyurea.

Impairment of Fertlllty:

HYUTIZ administered to male rats at 30 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

Hydroxyurea was embryotoxic and teratogenic in rats and rabbits at doses 0.8 times and 0.3 times, respectively, the maximum recommended human daily dose on a mg/m^2 basis.
In rats and dogs high dose of HYUTIZ reduced sperm production.

Nursing Mothers

HYUTIZ is excreted in human milk. Because of the potential for serious adverse reactions in a breastfed infant from hydroxyurea, including carcinogenicity, discontinue breastfeeding during treatment with HYUTIZ.
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 discontinuethe 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 HYUTIZ 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.

Renal Insufficiency

As renal excretion is a pathway of elimination, consideration

Size: 128 x 182 mm

should be given to decreasing the dosage of HYUTIZ 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.

Carcinogenesis, Mutagenesis, Impainnent of Fertility

HYUTIZ is genotoxic in a wide range of test systems and is thus presumed to be a human carcinogen. In patients receiving long-term for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported. It is unknown whether this leukemogenic effect is secondary to HYUTIZ

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

DRUG INTERACTIONS

The myelosuppressive activity may be potentiated by previous or concomitant radiotherapy or cytotoxic therapy. Fatal and non-fatal pancreatitis has occurred in HIV-infected patients during therapy with 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 HYUTIZ and other antiretroviral agents.Fatal hepatic events were reported most often in patients treated with the combination of hydroxycarbamide, didanosine and stavudine. Peripheral neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving HYUTIZ combination with antiretroviral agents, including didanosine, with or without stavudine.

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 hydroxycarbamide.

DOSAGE AND ADMINISTRATION

Adults

Treatment regimens can be continuous or intermittent. The continuous regimen is particularly sutiable for chronic myeloid leukaemia, while the intermittent regimen, with its diminished effect on the bone marrow, is more satisfactory for the management of cancer of the cervix. Hydroxyurea should be started 7 days before concurrent irradiation therapy. If Hydroxyurea is used concomitantly with radiotherapy, adjustment of radiation dosage is not usually necessary.

An adequate trial period for determining the antineoplastic effect of Hydroxyurea is six weeks. Where there is a significant clinical response therapy may be continued indefinitely, provided that the patient is kept under adequate observation and shows no unusual or severe reactions. Therapy should be interrupted if the white cell count drops below 2.5x109L or the platelet count below $100x10^9$/L.

Continuous therapy:

Hydroxyurea 20-30mg/kg should be given daily in single doses. Dosage should be based on the patient's actual or ideal weight, whichever is the less. Therapy should be monitored by repeat blood counts.

Intermittent therapy:

Hydroxyurea 80mg/kg in single doses should be given every third day. Using the intermittent regimes the likelihood of WBC depression is diminished, but if low counts are produced, 1 or more doses of Hydroxyurea should be omitted.

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

Children

Because of the rarity of these conditions in children, dosage regimens have not been established.

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

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. The contents of capsules should not be inhaled or allowed to come into contact with the skin or mucous membranes. Spillages must be wiped immediately.

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.

Handlln g & Dlsposal

Procedures for proper handling and disposal of anti neoplastic 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.

STORAGE

Store below 30°C.

SHELF LIFE

24months

HOW SUPPLIED

HYUTIZ 500

HYUTIZ 500 supplied in a bottle of 100 Capsules packed in a HDPE container

MANUFACTURED & MARKETED BY:

Tizig Pharma Private Limited

Factory: Tukucha, Nala-1, Banepa, Nepal.

Regd. Office: Maligaun-5, Kathmandu, Nepal.