141mm

Hydroxa 500mg 10 Capsules

(Hydroxyurea)

ہائیڈروکسا ۵۰۰ ملی گرام ۱۰ کیپسولز

(ہائی ڈرکسیوریا)

206mm

COMPOSITION

Each capsule contains:

Hydroxyurea 500mg

(USP Specifications)

DESCRIPTION

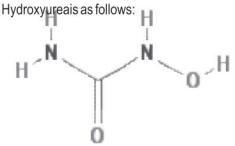
The active component of HYDROXA is hydroxyurea. Hydroxyurea, also called as hydroxycarbamide, is an anticancer drug. Hydroxyurea is an analog of urea. It is effective in the treatment of different cancers to slow or stop the abnormally growing cells. It belongs to the class of organic compounds known as organooxygen compounds. These are organic compounds containing a bond between a carbon atom and an oxygen atom Hydroxyurea is used in combination with different anticancer drugs to obtain best therapeutic effects and to reduce toxicity or side effects. Hydroxyureais administered orally.

MOLECULAR & STRUCTURAL FORMULA

Molecular formula of Hydroxyurea is as follows:

$CH_4N_2O_2$

Structural formula of Hydroxyureais as follows:



CLINICAL PHARMACOLOGY

MODE OF ACTION

Hydroxyurea is converted to a free radical nitroxide (NO) in vivo, and transported by diffusion into cells where it quenches the tyrosyl free radical at the active site of the M2 protein subunit of ribonucleotide reductase, inactivating the enzyme. The entire replicase complex, including ribonucleotide reductase, is inactivated and DNA synthesis is selectively inhibited, producing cell death in S phase and synchronization of the fraction of cells that survive. Repair of DNA damaged by chemicals or irradiation is also inhibited by hydroxyurea, offering potential synergy between hydroxyurea and radiation or alkylating agents. Hydroxyurea also increases the level of fetal hemoglobin, leading to a reduction in the incidence of vasoocclusive crises in sickle cell anemia. Levels of fetal hemoglobin increase in response to activation of soluble guanylyl cyclase (sGC) by hydroxyurea-derived NO.

INDICATIONS

HYDROXA is indicated for:

- Melanoma.
- Resistant chronic myelocytic leukemia.
- 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 & ADMINISTRATION

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 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.

Adjustment of irradiation dose is not usually necessary when hydroxyurea is used concomitantly.

Resistant Chronic Myelocytic Leukemia

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

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 60% of an oral dose undergoes conversion through metabolic pathways that are not fully characterized. One pathway is probably saturable hepatic metabolism. Another minor pathway may be degradation 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 likely a linear first-order renal process.

Special Populations.

Pediatric

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

Renal Insufficiency

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of hydroxyurea in patients with renal impairment. In adult patients with sickle cell disease, an open-label, non-randomized, single-dose, multicentre study was conducted to assess the influence of renal function on the pharmacokinetics of hydroxyurea. Patients in the study with normal renal function (creatinine clearance [CrCl] > 80 mUmin), mild (CrCl 50-80 mL/min), moderate (CrCl = 30- <50 mUmin), or severe (< 30 mUmin) renal impairment received hydroxyurea as a single oral dose of 15 mg/kg, achieved by using combinations of the 200 mg, 300 mg, or 400 mg capsules. Patients with end-stage renal disease(ESRD) received two doses of 15 mg/kg separated by 7 days, the first was given following a 4-hour hemodialysis session, the second prior to hemodialysis. In this study, the mean exposure (AUC) in patients whose creatinine clearance was < 60 mUmin (or ESRD) was approximately 64% higher than in patients with normal renal function. The results suggest that the initial dose of hydroxyurea should be reduced when used to treat 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.

PRECAUTIONS

General

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 countdecreases to less than 2500/mm3, or the platelet count to less than 100,000/mms, 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 should be used with caution in patients with marked renal dysfunction. 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 is recommended. Patients who develop signs and symptoms of pancreatitis should permanently discontinue therapy with hydroxyurea.

An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with hydroxyurea, and in particular, in combination with didanosine and stavudine. This combination should be avoided.

Special 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. 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.
- In HIV-infected patients during therapy with hydroxyurea and didanosine, with or without stavudine, fatal and nonfatal pancreatitis have occurred. 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 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 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 polycythaemia 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.

• Cutaneous vasculitis toxicities, including vasculitis 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.

Fertility, pregnancy and lactation

Pregnancy Category D

Drugs which affect DNA synthesis, such as hydroxycarbamide, 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. Since Hydroxa is a cytotoxic agent it has produced a teratogenic effect in some animal species.

In rats and dogs, high doses of hydroxycarbamide reduced sperm production. Hydroxycarbamide is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants from hydroxycarbamide, a decision should be made whether to discontinue nursing or to discontinue Hydroxa, taking into account the importance of the drug to the mother.

Hydroxa can cause fetal harm when administered to a pregnant woman. Hydroxa should not normally be administered to patients who are pregnant, or to mothers who are breast feeding, unless the potential benefits outweigh the possible hazards.

When appropriate both male and female patients should be counselled concerning the use of contraceptive measures before and during treatment with Hydroxa.

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.

SIDE EFFECTS

Bone-marrow suppression is the major toxic effect of hydroxycarbamide.

Cutaneous vasculitic toxicities including vasculitic ulcerations and gangrene have occurred in patients with myeloproliferative disorders during therapy with hydroxycarbamide. The risk of vasculitic toxicities is increased in patients who receive prior or concomitant interferon therapy.

In some patients, hyperpigmentation, atrophy of skin and nails, scaling, violet papules and alopecia have been observed following several years of long-term daily maintenance therapy with hydroxycarbamide.

Cases of fatal and non-fatal pancreatitis and hepatotoxicity and severe peripheral neuropathy have been observed in HIV patients when hydroxycarbamide was administered with antiretroviral agents, in particular didanosine plus stavudine. Patients treated with hydroxycarbamide in combination with didanosine, stavudine and indinavir showed a median decline in CD4 cells of approximately 100/mm3.

Adverse reactions observed with combined hydroxyurea and irradiation therapy were similar to those reported with the use of hydroxyurea alone, primarily bone marrow depression (leukopenia and anaemia) and gastric irritation. Nearly all patients receiving an adequate course of combined Hydroxa and irradiation therapy will develop leukopenia. Decreased platelet counts (<100,000/mm3) have occurred rarely and usually in the presence of marked leukopenia. Hydroxa may potentiate some adverse reactions usually seen with irradiation alone, such as gastric distress and mucositis.

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-Ifected patients during therapy with hydroxycarbamide 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 hydroxycarbamide and other antiretroviral agents. Fatal hepatic events were reported most often in patients treated with the combination of hydroxycarbamide, didanosine and stavudine. This combination should be avoided. Peripheral neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving hydroxycarbamide in combination with antiretroviral agents, including didanosine, with or without stavudine.
- Studies have shown that there is an analytical interference of hydroxycarbamide 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.
- There is an increased risk of severe or fatal infections with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients

CONTRAINDICATIONS

Hydroxyurea is contraindicated in patients:

- With marked bone marrow depression i.e. Leukopenia (<2500 WBC) or thrombocytopenia (< 100,000), or severe anemia.
- Who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation.

STORAGE & INSTRUCTIONS:

Store between 15-30°C.
Protect from heat, sunlight and moisture.
Keep away from the reach of children.
To be sold on the prescription of a registered oncologist or on demand from cancer hospitals and institutions only.

HOW SUPPLIED

Hydroxa Capsule 500mg
10 capsules.

خوراک وطریقہ استعمال:

سرطان کے ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۳۰ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دھوپ، گرمی اور نمی سے محفوظ رکھیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند کینسر ہسپتال یا انکولوجسٹ کے نسخہ پر فروخت کریں۔

Manufactured by:
PHARMASOL
PRIVATE LIMITED
Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.