Hydronix
Hydroxyurea

COMPOSITION
Hydronix Capsule: Each capsule contains Hydroxyurea USP 500 mg.

DESCRIPTION
Hydronix (Hydroxyurea Capsule) is an antineoplastic agent available for oral use as capsules providing 500 mg hydroxyurea.

CLINICAL PHARMACOLOGY
Mechanism of Action
The precise mechanism by which Hydroxyurea produces its cytotoxic and cytoreductive effects is not known. However, various studies support 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.
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.
The mechanisms by which Hydroxyurea produces its beneficial effects in patients with sickle cell anemia (SCA) are uncertain. Known pharmacologic effects of Hydronix that may contribute to its beneficial effects include increasing hemoglobin F levels in RBCs, decreasing neutrophils, increasing the water content of RBCs, increasing deformability of sickled cells and altering the adhesion of RBCs to endothelium.
The significant benefit is expected in beta-thalassemia by neutralized excess alpha-chains and increased production of gamma-chains which leads to decreased ineffective erythropoiesis and increasing HbF.

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. In adults with SCA, mean cumulative urinary recovery of Hydroxyurea was about 40% of the administered dose.

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 for SCA.

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, multicenter 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 mL/min), mild (CrCl 50-80 mL/min), moderate (CrCl = 30-<50 mL/min) or severe (<30 mL/min) 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 mL/min (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.

Drug Interactions
There are no data on concomitant use of Hydroxyurea with other drugs in humans.

INDICATIONS
Significant tumour response to Hydroxyurea has been demonstrated in melanoma, resistant chronic myeloid leukaemia and recurrent metastatic or inoperable carcinoma of the ovary. Hydronix 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.
Hydronix used in the management of β thalassemia, essential thrombocythemia and polycythemia vera.
Hydronix is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises.

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

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 to 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
Hydronix 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/m2 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
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 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 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility
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.
Nursing Mothers
Hydroxyurea is excreted in human milk. Because of the potential for serious adverse reactions with Hydroxyurea, a decision should be made either 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

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. 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.

Information for Patients
Patients should be reminded that this medication must be handled with care. People who are not taking Hydroxyurea should not be exposed to it. To decrease the risk of exposure, wear disposable gloves when handling Hydroxyurea Anyone handling Hydronix should wash their hands before and after contact with the capsules. 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. Contact your doctor for instructions on how to dispose of outdated capsules.

ADVERSE EFFECTS
Haematological
Adverse reactions have been primarily bone marrow depression (neutropenia, anaemia and occasionally thrombocytopenia).

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.

Others
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 .
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/mm^3.

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/mm^3) 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.

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

DOSAGE AND ADMINISTRATION
To minimize the risk of dermal exposure, always wear impervious gloves when handling Hydroxyurea capsules. Hydroxyurea capsules should not be opened. Personnel should avoid exposure to crushed or opened capsules. If contact with crushed or opened capsules occurs, wash immediately and thoroughly. More information is available in the references listed below.
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 Hydroxyurea with other myelosuppressive agents may require adjustment of dosages. Since Hydroxyurea may raise the serum uric acid level, dosage adjustment of uricosuric medication may be necessary.

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.
Irradiation should be given at the maximum dose considered appropriate for the particular therapeutic situation; adjustment of irradiation dosage is not usually necessary when Hydroxyurea is used concomitantly.

Resistant Chronic Myelocytic Leukemia
Until the intermittent therapy regimen has been evaluated, Conitunous Therapy 20-30 mg/kg administered orally as a single dose daily is recommended.

Polycythemia Vera
Dosage regimens for the treatment of p. vera may be initiated at 30mg/kg for one week, followed by 15-20mg/kg daily.

Essential Thrombocythemia
Initial dose of hydroxyurea is about 15mg/kg per day. Doses are subsequently adjusted according to platelet counts.

Sickle-cell disease
The initial dose of Hydronix is 15 mg/kg/day as a single dose. The patient's blood count must be monitored every two weeks. If blood counts are in an acceptable range*, the dose may be increased by 5 mg/kg/day every 12 weeks until a maximum tolerated dose (the highest dose that does not produce toxic** blood counts over 24 consecutive weeks), or 35 mg/kg/day, is reached. If blood counts are between the acceptable range* and toxic**, the dose is not increased. If blood counts are considered toxic**, Hydronix should be discontinued until hematologic recovery. Treatment may then be resumed after reducing the dose by 2.5 mg/kg/day from the dose associated with hematologic toxicity. Hydronix may then be titrated up or down, every 12 weeks in 2.5 mg/kg/day increments, until the patient is at a stable dose that does not result in hematologic toxicity for 24 weeks. Any dosage on which a patient develops hematologic toxicity twice should not be tried again.

*acceptable range =
neutrophils≥2500 cells/mm^3,
platelets≥95,000/mm^3,
hemoglobin >5.3 g/dL and
reticulocytes≥95,000/mm^3 if the hemoglobin concentration <9 g/dL.

**toxic =
neutrophils <2000 cells/mm^3,
platelets <80,000/mm^3,
hemoglobin <4.5 g/dL and
reticulocytes <80,000/mm3 if the hemoglobin concentration <9 g/dL.

β-thalassemia patients
15-30 mg/kg administered orally as a single dose daily

Renal Dose Adjustments
Renal Dose Adjustments for Adults:

Sickle cell anemia:
CrCl 60 mL/minute or Greater: Initial dose: 15 mg/kg/day
CrCl Less than 60 mL/minute: Reduce initial dose to 7.5 mg/kg/day

Other indications:
CrCl 10 to 50 mL/minute: 50% of normal dose
CrCl Less than 10 mL/minute: 20% of normal dose

Hepatic Dose Adjustment
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.

PHARMACEUTICAL INFORMATION
Storage Condition
Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging
Hydronix Capsule: Each commercial box contains 7 x 4's capsules in Alu-Alu blister pack.

Manufactured By
BEACON
Pharmaceuticals Limited
Mymensingh, Bangladesh

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