PRODUCT MONOGRAPH

[Pr]APO-HYDROXYUREA

Hydroxyurea Capsules USP

500 mg

Antineoplastic Agent

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9

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Hydroxyurea Capsules USP
500 mg

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

APO-HYDROXYUREA (HYDROXYUREA) SHOULD BE ADMINISTERED UNDER THE SUPERVISION OF A PHYSICIAN EXPERIENCED IN THE USE OF CANCER CHEMOTHERAPEUTIC AGENTS.

ACTIONS AND CLINICAL PHARMACOLOGY

Neoplastic Disease: The precise mechanism by which hydroxyurea produces its antineoplastic effects cannot, at present, be described. However, the reports of various studies in rat and human tissue cultures 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. Hydroxyurea probably acts by decreasing the rate of conversion of ribonucleotides and deoxyribonucleotides. This effect is particularly apparent in cells with a high rate of proliferation.

Potentiation of Irradiation Therapy: Three mechanisms have been postulated for the potentiation of the therapeutic effects of irradiation by hydroxyurea on squamous cell (epidermoid) carcinomas of the head and neck. *In vitro* studies utilizing Chinese hamster cells suggest that hydroxyurea is lethal to normally radioresistant S-stage cells and 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; there is no alteration of RNA and protein syntheses.

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 area under the plasma concentration-time curve (AUC) 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. Hydroxyurea crosses the blood-brain barrier.

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 to

acetohydroxamic acid by urease found in intestinal bacteria.

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. In patients with malignancies, renal elimination ranged from 25 to 55% of the administered dose. The concentration in the serum at 24 hours is negligible when the usual dose is given as a single daily dose.

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

Renal Insufficiency: Since renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage in this population. In adult patients with sickle cell disease, an open-label, non-randomized, single dose, multi-center study was conducted to assess the influence of renal function on the pharmacokinetics of hydroxyurea. Patients in the study with normal (creatinine clearance (CrCl) > 80 ml/min), mild (CrCl 50-80 ml/min), or severe (CrCl < 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 (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: There are no data that support specific guidance for dosage adjustment in patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).

Comparative Bioavailability

Comparative, bioavailability studies were performed on healthy human volunteers under fasting and fed conditions. The rate and extent of absorption of hydroxyurea was measured and compared following a single oral 500 mg dose of APO-HYDROXYUREA (hydroxyurea) or Hydrea® capsules. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data
Hydroxyurea (Dose: 1 x 500 mg) From Measured Data - Under Fasting Conditions
Based on Hydroxyurea

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	APO–HYDROXYUREA	Hydrea®†	
AUC_T (µg.h/mL)	37.1 37.7 (19)	36.4 36.8 (15)	102.0
AUC_I (µg.h/mL)	41.6 42.1 (17)	40.8 41.2 (15)	101.9
C_{MAX} (µg/mL)	9.22 9.41 (22)	9.49 9.74 (25)	97.2

T_{MAX}* (h)	0.74 (36)	0.66 (44)	
$t_{½}$* (h)	4.24 (31)	4.44 (33)	

* Arithmetic means (CV%).
** Based on the least squares estimate.
† Hydrea® is marketed by Squibb Canada Inc., a part of Bristol-Myers Squibb Canada Inc.

Summary Table of the Comparative Bioavailability Data
Hydroxyurea (Dose: 1 x 500 mg) From Measured Data - Under Fed Conditions
Based on Hydroxyurea

Parameter	Geometric Mean Arithmetic Mean (CV%) APO–HYDROXYUREA	 Hydrea®†	Ratio of Geometric Means (%)**
AUC_T (µg.h/mL)	36.0 36.4 (13)	36.2 36.5 (12)	99.4
AUC_I (µg.h/mL)	39.8 40.1 (12)	39.7 40.0 (11)	99.8
C_{MAX} (µg/mL)	7.04 7.14 (16)	6.79 6.88 (18)	103.9
T_{MAX}* (h)	2.42 (29)	2.19 (34)	
$t_{½}$* (h)	3.32 (17)	3.45 (19)	

* Arithmetic means (CV%).
** Based on the least squares estimate.
† Hydrea® is marketed by Squibb Canada Inc., a part of Bristol-Myers Squibb Canada Inc.

INDICATIONS AND CLINICAL USE

APO-HYDROXYUREA (hydroxyurea) is indicated for concomitant use with irradiation therapy in the treatment of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip.

Tumor responses to hydroxyurea have been reported in resistant chronic myelocytic leukemia.

CONTRAINDICATIONS

APO-HYDROXYUREA (hydroxyurea) is contraindicated in patients with marked bone marrow depression, i.e., leukopenia (< 2500 WBC/mm^3) or thrombocytopenia (< 100,000/mm^3), or severe anemia; or in patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation.

WARNINGS

APO-HYDROXYUREA (hydroxyurea) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Treatment with APO-HYDROXYUREA (hydroxyurea) should not be initiated if bone marrow function is depressed (see CONTRAINDICATIONS). APO-HYDROXYUREA may produce bone marrow suppression; leukopenia is generally its first and most common manifestation. Thrombocytopenia and anemia occur less often and are seldom seen without a preceding

leukopenia. The recovery from myelosuppression is rapid when APO-HYDROXYUREA therapy is interrupted. Bone marrow depression is more likely in patients who have previously received radiotherapy or cytotoxic cancer chemotherapeutic agents; APO-HYDROXYUREA should be used cautiously in such patients.

Severe anemia must be corrected before initiating therapy with APO-HYDROXYUREA.

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 anemia, but is not related to vitamin B_{12} or folic acid deficiency. The macrocytosis may mask the incidental development of folic acid deficiency; regular determinations of serum folic acid are recommended. 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.

Patients who have received irradiation therapy in the past may have an exacerbation of post irradiation erythema when APO-HYDROXYUREA is given.

Geriatric Use

Elderly patients may be more sensitive to the effects of APO-HYDROXYUREA and may require a lower dose regimen.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Hydroxyurea is unequivocally genotoxic and a presumed transpecies carcinogen which implies a carcinogenic risk to humans. In patients receiving long-term therapy with hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocytopenia, secondary leukemia has been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or is associated with the patients' underlying disease. Skin cancer has also been reported in patients receiving long-term hydroxyurea.

Azoospermia or oligospermia, sometimes reversible, have been observed in men. Male patients should be informed about the possibility of sperm conservation before the start of therapy.

As hydroxyurea is genotoxic, men under therapy are advised to use safe contraceptive measures during and at least 1 year after therapy.

Use in Pregnancy

Hydroxyurea has been demonstrated to be a potent teratogen in a wide variety of animal models, including mice, rats, hamsters, rabbits, cats, miniature swine, dogs, and monkeys. The spectrum of effects following prenatal exposure to hydroxyurea includes embryo-fetal death, numerous fetal malformations of the viscera and skeleton, growth retardation, and functional deficits.

APO-HYDROXYUREA (hydroxyurea) can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If APO-HYDROXYUREA is used during pregnancy or if the patient becomes pregnant while on APO-

HYDROXYUREA therapy, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking APO-HYDROXYUREA.

APO-HYDROXYUREA should not be used to treat males contemplating conception.

Vaccinations

Concomitant use of APO-HYDROXYUREA with a live virus vaccine may potentiate the replication of the vaccine virus because normal defense mechanisms may be suppressed by APO-HYDROXYUREA.

Vaccination with a live vaccine in a patient taking APO-HYDROXYUREA may result in severe infection. Patient's antibody response to vaccines, including killed or inactivated vaccines, may be suboptimal. The use of live vaccines should be avoided and individual specialist advice sought (see DRUG INTERACTIONS).

Drug-Induced Fever

High fever (≥ 39°C) requiring hospitalization has been reported, in some cases concurrently with gastrointestinal, pulmonary, musculoskeletal, hepatobiliary, dermatological or cardiovascular manifestations. Onset typically occurred within 6 weeks of initiation and resolved promptly after discontinuation of hydroxyurea. Upon re-administration fever re-occurred within 24 hours.

Hepatic

Hepatitis and cholestasis have been reported commonly in patients treated with hydroxyurea, with many requiring hospitalization. If hepatitis or cholestasis occurs, APO-HYDROXYUREA should be discontinued (see ADVERSE EVENTS).

Hepatotoxicity and hepatic failure resulting in death were 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.

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported in patients taking hydroxyurea therapy. Patients at risk of tumor lysis syndrome are those with the highest tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

Respiratory

Interstitial lung disease including pulmonary fibrosis, lung infiltration, pneumonitis, and alveolitis/allergic alveolitis (including fatal cases) have been reported in patients treated with hydroxyurea for myeloproliferative neoplasm. Patients developing pyrexia, cough, dyspnea, or

other respiratory symptoms should be closely monitored, investigated and treated. Promptly discontinue hydroxyurea and treat with corticosteroids to resolve the pulmonary events (see ADVERSE EVENTS).

Other

Fatal and nonfatal pancreatitis has occurred in HIV-infected patients during therapy with hydroxyurea and didanosine, with or without 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 (see ADVERSE EVENTS).

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 (see ADVERSE EVENTS: Dermatologic).

PRECAUTIONS

Renal Insufficiency

APO-HYDROXYUREA (hydroxyurea) should be used with caution in patients with renal dysfunction (see DOSAGE and ADMINISTRATION).

Use in Children

Safety and effectiveness of APO-HYDROXYUREA in children have not been established.

Nursing Mothers

Hydroxyurea is secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from hydroxyurea, breast feeding should be discontinued.

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.

A published study has shown increases of laboratory values of urea, uric acid (5 to 9%) and lactic acid (6 to 11%) measured by *in vitro* enzymatic assays, in the presence of hydroxyurea (0.1 to 1 mM), indicating an analytical interference. The clinical relevance of these results is unknown.

In vitro studies have shown a significant increase in cytarabine cytotoxic activity in hydroxyurea-treated cells. Whether this interaction will lead to synergistic toxicity in the clinical setting or the need to modify cytarabine doses has not been established.

There is increased risk of serious and fatal infections with the concomitant use of live vaccines. Live vaccines are not recommended in patients treated with APO-HYDROXYUREA (see WARNINGS - Vaccinations).

Driving/Operating Machinery

The effect of APO-HYDROXYUREA on driving and operating machinery has not been studied. Since APO-HYDROXYUREA may cause drowsiness and other neurologic effects (see ADVERSE REACTIONS, Neurologic), alertness may be impaired.

Information for Patients

Patients should be informed to maintain adequate fluid intake. The physician should be consulted regarding missed doses.

ADVERSE REACTIONS

Hematologic

Bone marrow depression (leukopenia, anemia, and occasionally thrombocytopenia) (see WARNINGS).

Gastrointestinal

Stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation.

Dermatologic

Maculopapular rash, facial erythema, peripheral erythema, skin ulceration, cutaneous lupus erythematosus and dermatomyositis like skin changes. Nail pigmentation (melanonychia) has been observed in some patients. 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 been reported rarely.

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. (see WARNINGS).

Neurologic

Drowsiness, rare instances of headache, dizziness, disorientation, hallucinations, and convulsions. Their relationship to hydroxyurea administration is questionable because cerebral metastatic disease was not excluded.

Renal

Elevated serum uric acid, BUN, and creatinine levels; rare instances of dysuria. Abnormal BSP retention has been reported.

Hepatic

Hepatitis and cholestasis have been reported commonly in patients treated with hydroxyurea with many requiring hospitalization. If hepatitis or cholestasis occurs APO-HYDROXYUREA should be discontinued. Elevation of hepatic enzymes have been reported.

Fatal and nonfatal hepatotoxicity have been reported in HIV-infected patients who received hydroxyurea in combination with antiretroviral agents, in particular didanosine plus stavudine.

Musculoskeletal and connective tissue disorders

Systemic lupus erythematosus.

Respiratory

Interstitial lung disease, pneumonitis, alveolitis, allergic alveolitis, cough.

Other

Fever, chills, malaise, asthenia, azoospermia, oligospermia, tumor lysis syndrome and rare instances of acute pulmonary reactions (diffuse pulmonary infiltrates/fibrosis, and dyspnea). Fatal and nonfatal pancreatitis 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).

Combined Hydroxyurea and Irradiation Therapy

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 anemia), and gastric irritation. Nearly all patients receiving an adequate course of combined hydroxyurea and irradiation therapy will develop leukopenia. Decreased platelet counts (< 100,000 cells/mm^3) have occurred rarely and usually in the presence of marked leukopenia. APO–HYDROXYUREA may potentiate some adverse reactions usually seen with irradiation alone, such as gastric distress and mucositis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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

DOSAGE AND ADMINISTRATION

Because of the rarity of carcinomas of the head and neck in children, dosage regimens have not been established.

Dosage regimens in the treatment of the neoplastic diseases should be based on the patient's actual or ideal weight, whichever is less.

Solid Tumors

Intermittent Therapy: 80 mg/kg administered orally as a ***single*** dose every ***third*** day.

This intermittent dosage schedule may offer the advantage of reduced toxicity over daily therapy (e.g., bone marrow depression).

Concomitant Therapy with Irradiation (Carcinoma of the head and neck): 80 mg/kg administered orally as a ***single*** dose every ***third*** day.

Administration of APO-HYDROXYUREA (hydroxyurea) should be started at least seven days before initiation of irradiation, and continued during radiotherapy and continue indefinitely thereafter, provided the patient is kept under adequate observation and exhibits no unusual or severe toxicity.

Resistant Chronic Myelocytic Leukemia

Continuous Therapy
20 to 30 mg/kg administered orally as a single daily dose.

An adequate trial period for determining the effectiveness of APO-HYDROXYUREA is 6 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/mm^3, or the platelet count below 100,000/mm^3. In these cases, the counts should be reevaluated after 3 days, and therapy resumed when the counts return to acceptable levels. Hematopoietic rebound is usually rapid. If rapid rebound has not occurred during combined APO-HYDROXYUREA and irradiation therapy, irradiation may also be interrupted. Anemia, even if severe can be managed without interrupting APO-HYDROXYUREA therapy.

APO-HYDROXYUREA should be administered cautiously to patients who have recently received extensive radiation therapy or chemotherapy with other cytotoxic drugs (see WARNINGS and ADVERSE EVENTS).

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, APO-HYDROXYUREA therapy may be temporarily interrupted; if it is extremely severe, irradiation dosage may, in addition, be temporarily postponed.

Severe gastric distress, such as nausea, vomiting, and anorexia, resulting from combined therapy may usually be controlled by interruption of APO-HYDROXYUREA administration.

DOSAGE ADJUSTMENT

Concurrent use of APO-HYDROXYUREA with other myelosuppressive agents may require adjustments of dosages.

Renal Insufficiency: There are no data that support specific guidance for dosage adjustment in patients with impaired renal function. Since renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage in this population. Close monitoring of hematologic parameters is advised.

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

INSTRUCTIONS FOR USE, HANDLING and DISPOSAL

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 (see PRECAUTIONS, Information for Patients). Some inert material used as a vehicle in the capsule may not dissolve, and float on the surface.

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 APO-

HYDROXYUREA should not be exposed to it. To decrease the risk of exposure, wear disposable gloves when handling APO-HYDROXYUREA or bottles containing APO-HYDROXYUREA. Anyone handling APO-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 disposable towel and discarded in a closed container, such as a plastic bag, as should the empty capsules. APO-HYDROXYUREA should be kept away from children and pets.

To minimize the risk of dermal exposure, always wear impervious gloves when handling bottles containing APO-HYDROXYUREA capsules. This includes 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.

Procedures for proper handling and disposal of anticancer 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.

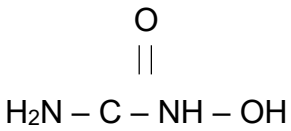
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Hydroxyurea

Chemical Name: 1) carbamyl hydroxylamine
2) hydroxycarbamide

Structural Formula:



Molecular Formula: $CH_4N_2O_2$

Molecular Weight: 76.05 g/mol

Description: Hydroxyurea is an essentially tasteless, white crystalline powder, freely soluble in water and hot alcohol.

Composition

In addition to hydroxyurea, each capsule contains the non-medicinal ingredients methylcellulose and stearic acid. The capsule shell contains the non-medicinal ingredients, D&C red #28, D&C red #33, FD&C blue #1, FD&C red #40, FDA/E172 black iron oxide, FDA/E172 yellow iron oxide, gelatin and titanium dioxide. The edible black imprinting ink contains the non-medicinal colouring agent black iron oxide.

Stability and Storage Recommendations

APO-HYDROXYUREA (hydroxyurea) should be stored at room temperature (15°C to 30°C). Protect from excessive heat and moisture.

AVAILABILITY OF DOSAGE FORMS

APO-HYDROXYUREA (hydroxyurea) is available in pink/turquoise capsules, imprinted with "APO 500" in black edible ink and containing 500 mg hydroxyurea. Available in bottles of 100s and blisters of 30s (3 × 10).

PHARMACOLOGY

Animal

Animal studies confirm that hydroxyurea is promptly and completely absorbed from the gastrointestinal tract. Studies with radioactive hydroxyurea administered orally or intraperitoneally to mice and rats showed that 75% of the radioactivity is recovered in the urine, with trace amounts found in the feces after 24 hours. 55% of the intraperitoneal dose in mice is metabolized to urea and carbon dioxide while 45% is excreted unchanged.

Intravenous administration to rats showed that hydroxyurea is rapidly equilibrated throughout body fluids and is rapidly excreted in urine. Plasma concentration in this study was found to decay exponentially. The proportion of drug recovered in the urine increased with the dose given.

Intravenous administration of a single dose of 100 mg/kg to a dog resulted in serum levels of 130, 110, 80 and 80 mcg/mL at 15, 30, 60 and 120 minutes respectively. Levels in the cerebrospinal fluid were 10, 20 and 30 mcg/mL at 30, 60 and 120 minutes, respectively.

TOXICOLOGY

Acute Toxicity

Species	Sex	Formulation	Route of Administration	LD_{50} (g/kg)
Mice	M	10% in water	Oral	7.3
Mice	M/F	10% in water	Oral	5
Mice	M	10% in water	I.P.	7.3
Mice	M/F	10 - 12% in water	I.V.	>15
Rats	M	10 or 30% in water	Oral	5.8
Rats	M	10% in saline	I.V.	4.7
Dogs	M	Capsules	Oral	Not lethal at a dose of 2.0
Dogs	M/F	10% in saline	I.V.	Not lethal at doses of 0.1 to 4.0

Signs of toxicity in mice included: excitement followed by sedation, ataxia, tremors, convulsions.

In rats, toxicity was manifested by: excitement followed by sedation, tremors, ataxia, convulsions, loss of weight, rigidity, apnea.

Signs of toxicity in dogs were: panting, ataxia, defecation, emesis, unsteady gait, mydriasis,

weakness of the hind limbs, hypothermia, bradycardia, decreased sensitivity to pain, loss of scratch reflex and eventually a plane 3 anesthesia.

Subacute and Chronic Toxicity

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. Thymic atrophy, weight depression and a tendency to bronchopulmonary infections were also noted. In the mouse, weight losses were more pronounced with daily therapy than with intermittent treatment. 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 or 140 to 1260 mg/kg/week given during 3 or 7 days a week 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. Changes in heart rate, blood pressure, orthostatic hypotension, electrocardiogram changes, and slight hemolysis, and/or methemoglobinemia) were observed in some species of laboratory animals at doses exceeding those used clinically.

Effect on Reproduction and Mutagenesis

Studies on rats given aqueous solutions of hydroxyurea orally revealed temporarily decreased fertility in male F_o generation rats due to aspermatogenesis. In F_o generation female rats there were no drug induced adverse effects on implantation of the number of live fetuses, viability or lactation. The administration of hydroxyurea did not induce mutagenic responses.

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CONSUMER INFORMATION

[Pr]APO-HYDROXYUREA

Hydroxyurea Capsules USP

This leaflet is a summary and will not tell you everything about APO-HYDROXYUREA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
APO-HYDROXYUREA (hydroxyurea) is used in combination with radiation to treat cancer of the head and neck, not including the lips. It is also used to treat a type of blood cancer that no longer responds to previous treatments. This type of cancer is called resistant chronic myelocytic leukemia.

What it does:
APO-HYDROXYUREA seems to interfere with the growth of cancer cells by preventing them from dividing.

When it should not be used:
APO-HYDROXYUREA should not be used if:

- you have problems with your bone marrow (low blood count e.g. severe anemia)
- you are sensitive/allergic to hydroxyurea or any other component of this medication. Tell your doctor if you think you have had an allergic reaction to any of these ingredients.

What the medicinal ingredient is:
Hydroxyurea.

What the important nonmedicinal ingredients are:
The non-medicinal ingredients are: methylcellulose and stearic acid.

The capsule shell contains the non-medicinal ingredients, D&C red #28, D&C red #33, FD&C blue #1, FD&C red #40, FDA/E172 black iron oxide, FDA/E172 yellow iron oxide, gelatin and titanium dioxide. The edible black imprinting ink contains the non-medicinal colouring agent black iron oxide.

What dosage forms it comes in:
APO-HYDROXYUREA is available in capsules containing 500 mg hydroxyurea.

WARNINGS AND PRECAUTIONS

BEFORE you use APO-HYDROXYUREA talk to your doctor or pharmacist if:

- you have problems with your kidneys**.** This because the dose of APO-HYDROXYUREA may need to be adjusted.
- you have received radiation therapy. This is because your chances of developing redness of the skin are higher if APO-HYDROXYUREA is used with radiation treatment.
- you have HIV/AIDS and are receiving treatment. This can increase your chances of developing:
  - pancreatitis (inflammation of the pancreas) and liver problems, or
  - peripheral neuropathy (pins and needles in your hands and feet).
- you recently received or are planning to receive a vaccination. Patients taking APO-HYDROXYUREA should not receive live vaccines.
- you are receiving treatment with interferon. Inflammation of the blood vessels of the skin, sometimes causing ulcers or death of the blood vessels has been reported. This is most common in patients who have received or are also currently receiving interferon treatment.
- Female patients:
  - If you are pregnant or planning to become pregnant, there are specific risk you must discuss with your doctor.
  - Avoid becoming pregnant while taking APO-HYDROXYUREA. It may harm your unborn child.
  - If you do become pregnant while taking APO-HYDROXYUREA, tell your doctor right away.
  - APO-HYDROXYUREA can pass into your breastmilk and harm your baby. Do not breastfeed while you are taking APO-HYDROXYUREA.
- Male patients who want to father a child:
  - APO-HYDROXYUREA may affect your fertility by causing an absence or low number of sperm in your semen. These effects may or may not return to normal. Damage to the genetic material (DNA) in your sperm is also possible.
  - If you want to have a child, talk to your doctor about preserving some semen prior to your treatment with APO-HYDROXYUREA.
  - Avoid fathering a child during treatment. Use effective methods of birth control during your treatment with APO-HYDROXYUREA and for at least one year after your last dose.

- Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to APO-HYDROXYUREA. If you feel drowsy, dizzy weak or tired, do not drive or use tools or machines.
- Tumour Lysis Syndrome (TLS): This side effect can be caused by APO-HYDROXYUREA. It is a complication of the breakdown of cancer cells. It is serious and can lead to death. Your doctor will monitor you for signs of TLS.
- A group of disorders that inflame or scar the lung tissue have occurred in patients taking hydroxyurea. This is called interstitial lung disease (ILD). Your doctor will monitor you for signs of ILD. These include fever, cough, shortness of breath and other respiratory symptoms.
- Hydroxyurea, the active ingredient in APO-HYDROXYUREA, may cause cancer and damage to the genetic material in cells (DNA).

INTERACTIONS WITH THIS MEDICATION

Make sure you talk to your doctor about all medications you are taking, including prescription, non-prescription, and herbal and/or natural products.
The following may interact with APO-HYDROXYUREA:

- Cytarabine, a chemotherapy drug used to treat some cancers.
- Medicines used to treat gout.
- Medicines that can affect your blood. This is because using APO-HYDROXYUREA at the same time as these medicines will increase your risk for side effects including low blood counts.

PROPER USE OF THIS MEDICATION

While you are using this medicine, your doctor may want you to drink extra fluids so that you will pass more urine. This will help prevent kidney problems and keep your kidneys working well.

Usual dose:
The dose of APO-HYDROXYUREA will be different for different patients. The dose you are to take will depend on what this medicine is being used to treat, your weight, and whether or not you are also taking other medicines.

Depending on your condition, the usual dose could be 80 mg/kg, or 20 to 30 mg/kg given by mouth. How often you take APO-HYDROXYUREA will also depend on the type of disease you have.

Take APO-HYDROXYUREA exactly as your doctor has indicated.
If you cannot swallow the APO-HYDROXYUREA capsules, your healthcare professional can provide you with instructions on another way to take this medicine.

Your doctor may interrupt, change your dose or stop your treatment. This will depend on your disease, how you are feeling and the type of side effects you experience.

Overdose:

If you think you have taken too much APO-HYDROXYUREA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

The following side effects have been reported in patients who have taken higher doses of hydroxyurea:

- infections of the skin and mucous membranes (inside the mouth, genitals, skinfolds)
- soreness, redness, swelling and peeling of skin on the palms and soles of feet
- changes in the colour of the skin
- mouth sores

Missed Dose:
It you miss a dose of this medicine check with your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, APO-HYDROXYUREA can cause side effects. These are not all the possible side effects that may be experienced when taking APO-HYDROXYUREA. If you experience any side effects including some that are not listed here, contact your doctor.

- Rash, redness and ulceration in the face, skin or extremities.
- Skin or nail changes.
- Muscle aches and a general, unwell feeling or malaise.
- Fatigue.

Tell your doctor immediately if you have a high fever (≥39°C) within 6 weeks of taking APO-HYDROXYUREA. The high fever can sometimes come with stomach, lung, muscle, liver, skin or heart

problems.

APO-HYDROXYUREA can cause abnormal blood test results. Your doctor will decide when to perform blood tests. Your doctor will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
	Only if severe	**In all cases**	
Common			
Stomatitis (inflammation in or around the mouth): mouth sores, redness and swelling of the lining of the mouth	X		
Nausea	X		
Vomiting	X		
Diarrhea	X		
Constipation	X		
Cholestasis (decrease in flow of bile from the liver): dark urine, clay-colored or white stools, itchiness, nausea, vomiting, inability to digest certain foods, pain in right upper part of the abdomen, yellow skin or eyes			X
Hepatitis (inflammation of the liver): yellowing of the skin and eyes, feeling tired, stomach ache, fever, nausea, diarrhea, no appetite, fever, headaches			X
Uncommon			
Loss of appetite	X		
Joint pain		X	
Drowsiness: feeling abnormally sleepy or tired during the day	X		
Headache: pain and discomfort in the head, scalp, or neck	X		
Dizziness: feeling faint, woozy, weak or unsteady	X		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
	Only if severe	**In all cases**	
Disorientation: losing sense of orientation, may not know their location and identity, or the time and date		X	
Convulsions: sudden, violent, irregular movement of the body		X	
Hallucinations: seeing, feeling or hearing things that are not real		X	
Kidney problems: Bloody or discolored urine, or increase in frequency of urination and pain in the sides where the kidneys are located		X	
Rare			
Diffuse pulmonary infiltrates/ fibrosis (when substances thicker than air, like pus, blood, or protein, remain in the lungs): dry painful cough, fever, difficulty breathing, fast shallow breathing			X
Dyspnea (shortness of breath): intense tightening in the chest, difficulty breathing, feeling of suffocation			X
Tumor lysis syndrome (the sudden, rapid death of cancer cells due to the treatment): lack of urination, severe muscle weakness, abnormal heartbeat, seizures			X
Cutaneous vasculitis (inflammation of blood vessels of the skin): skin redness/purple		X	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
	Only if severe	**In all cases**	
coloration, tiny colored spots, sores, and/or ulcers, sometimes with joint pain and/or fever, death, if you have been or, are currently being, treated with interferon.			
Unknown			
Interstitial lung disease (disorders that inflame or scar the lung tissue): shortness of breath when at rest, which gets worse with exertion; dry cough			X
Systemic lupus (condition that occurs when your body's immune system attacks your own tissues and organs): fever, joint pain, muscle pain; pain when breathing, sharp chest pain, bruising, tender red lumps usually on the shins, itchy red skin when exposed to light		X	
Cutaneous lupus (a form of systemic lupus that only affects the skin): scaly ring-like rash (redness with clear center), red patches on the skin, sensitivity to sunlight, rash on the face usually on cheeks and bridge of nose, ulcers in the mouth		X	

This is not a complete list of side effects. For any unexpected effects while taking APO-HYDROXYUREA, contact your doctor or pharmacist.

HOW TO STORE IT

APO-HYDROXYUREA should be stored at room temperature (15°C to 30°C). Protect from excessive heat and moisture.

Keep out of reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about APO-HYDROXYUREA:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); find the Consumer Information on the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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