PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrAPO-HYDROXYUREA

Hydroxyurea Capsules

Capsules, 500 mg, Oral

USP

Antineoplastic Agent

APOTEX INC
150 Signet Drive
Toronto, Ontario
M9L 1T9

Date of Initial Authorization:
SEP 18, 2003

Date of Revision:
February 28, 2025

Submission Control Number: 292677

RECENT MAJOR LABEL CHANGES

1 INDICATIONS	06/2023
7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis	06/2023
7 WARNINGS AND PRECAUTIONS, HEMATOLOGIC	06/2023
7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential	06/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: Data on which the indication was originally approved are not available; therefore, it is unknown if use in the geriatric population is associated with differences in safety or efficacy.

2 CONTRAINDICATIONS

- APO-HYDROXYUREA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- APO-HYDROXYUREA is contraindicated in patients with marked bone marrow depression, i.e., leukopenia (< 2500 white blood cells/mm^3) or thrombocytopenia (< 100,000/mm^3), or severe anemia.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- APO-HYDROXYUREA should be administered under the supervision of an adequately trained healthcare professional.
- Patients should be informed to maintain adequate fluid intake

4.2 Recommended Dose and Dosage Adjustment

Primary Squamous Cell (Epidermoid) Carcinomas of the Head and Neck)

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 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 re-evaluated 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.

Concomitant therapy

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

APO-HYDROXYUREA should be administered cautiously to patients who have recently received extensive radiation therapy or chemotherapy with other cytotoxic drugs (see 7 WARNINGS AND PRECAUTIONS, Hematologic and 8.5 Post-Market Adverse Reactions).

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.

Special Populations

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 (see 10.3 Pharmacokinetics). 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.

Pediatric patients (below 18 years):

Because of the rarity of carcinomas of the head and neck in children, dosage regimens have not been established. Health Canada has not authorized an indication for pediatric use.

Geriatric

Elderly patients may require a lower dose regimen (see 7 WARNINGS AND PRECAUTIONS)

4.4 Administration

If the patient prefers, or is unable to swallow capsules, the contents of the capsules may be emptied into a glass of water and taken immediately. Some inert material used as a vehicle in the capsule may not dissolve, and float on the surface.

4.5 Missed Dose

The physician should be consulted regarding missed doses.

5 OVERDOSAGE

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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Capsule 500 mg	Methylcellulose, stearic acid and talc. Capsule shell: 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. edible black imprinting ink: black iron oxide, potassium hydroxide, propylene glycol, shellac and strong ammonia solution.

Description
APO-HYDROXYUREA (hydroxyurea) is available in pink opaque body / turquoise opaque cap, hard-gelatin capsules, imprinted with “APO 500” in black edible ink, filled with homogenous white powder fill and containing 500 mg hydroxyurea. Available in bottles of 100s and blisters of 30s (3 × 10).

7 WARNINGS AND PRECAUTIONS

General

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.

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.

Interference with Continuous Glucose Monitoring Systems: Hydroxyurea may falsely elevate sensor glucose results from certain continuous glucose monitoring (CGM) systems and may lead to hypoglycaemia if sensor glucose results are relied upon to dose insulin.
If a patient using a CGM is to be prescribed hydroxyurea, consult with the CGM prescriber about alternative glucose monitoring methods.

Carcinogenesis and Mutagenesis

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.

Patients should be advised to protect skin from sun exposure, conduct self-inspection of the skin and be screened for secondary malignancies during routine follow-up visits.

Driving and Operating Machinery

The effect of hydroxyurea on driving and operating machinery has not been studied. Since APO-HYDROXYUREA may cause drowsiness and other neurologic effects (see 8.5 Post-Market Adverse Reactions, Neurologic), alertness may be impaired. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hematologic

Treatment with APO-HYDROXYUREA should not be initiated if bone marrow function is depressed (see 2 CONTRAINDICATIONS). 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 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.

Serious cases of hemolytic anemia in patients treated with hydroxyurea for myeloproliferative diseases have been reported (see 8.5 Post-Market Adverse Reactions). Patients who develop persistent anemia should have laboratory tests evaluated for hemolysis. In the setting of confirmed diagnosis of hemolytic anemia, APO-HYDROXYUREA should be discontinued.

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 B12 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.

Hepatic/Biliary/Pancreatic

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 8 ADVERSE REACTIONS).

Hepatotoxicity and hepatic failure resulting in death were reported during post-marketing surveillance in human immunodeficiency virus (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.

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.

Immune

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 9.2 Drug Interactions Overview).

Neurologic

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 8.5 Post-Market Adverse Reactions, Neurologic).

Renal

APO-HYDROXYUREA should be used with caution in patients with renal dysfunction (see 4.2 Recommended Dose and Dosage Adjustment and 10.3 Pharmacokinetics).

Reproductive Health: Female and Male Potential

- **Fertility**

  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.

  Female patients of reproductive potential should be counselled to use effective contraception during therapy and for at least 6 months after therapy.

- **Teratogenic Risk**

  Animal studies have shown that effects of prenatal exposure to hydroxyurea included embryo-fetal death, numerous fetal malformations of the viscera and skeleton, growth retardation, and functional deficits (see 16 NON-CLINICAL TOXICOLOGY). Women of childbearing potential should be advised to avoid becoming pregnant while taking APO-HYDROXYUREA.

  As hydroxyurea is genotoxic, men under therapy are advised to use safe contraceptive measures during and at least 1 year after therapy. APO-HYDROXYUREA should not be used to treat males contemplating conception.

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 8.5 Post-Market Adverse Reactions, Respiratory).

Skin

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 8.5 Post-Market Adverse Reactions, Dermatologic).

7.1 Special Populations

7.1.1 Pregnant Women

Hydroxyurea can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. Animal studies have shown that prenatal exposure to hydroxyurea is associated with developmental abnormalities (see 16 NON-CLINICAL TOXICOLOGY). 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.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Pediatrics (< 18 years old): Safety and effectiveness in children have not been established. No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The data on which the indication was originally approved are not available.

8.2 Clinical Trial Adverse Reactions

The data on which the indication was originally approved are not available.

8.5 Post-Market Adverse Reactions

Hematologic

Bone marrow depression (leukopenia, anemia, and occasionally thrombocytopenia), hemolytic anemia (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

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 7 WARNINGS AND PRECAUTIONS, Skin).

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, blood urea nitrogen (BUN), and creatinine levels; rare instances of dysuria. Abnormal bromsulphalein test (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 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

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.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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 7 WARNINGS AND PRECAUTIONS, Hematologic and 8.5 Post-Market Adverse Reactions, Hematologic). 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 7 WARNINGS AND PRECAUTIONS, Immune)

9.4 Drug-Drug Interactions

Since hydroxyurea may raise the serum uric acid level, dosage adjustment of uricosuric medication may be necessary.

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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

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.

Hydroxyurea may falsely elevate sensor glucose results from certain continuous glucose monitoring (CGM) systems. (see 7 WARNINGS AND PRECAUTIONS).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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.

10.3 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.

Elimination

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 and Conditions

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

- **Hepatic Insufficiency**

  There are no data that support specific guidance for dosage adjustment in patients with impaired hepatic function.

- **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 to 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 7 WARNINGS AND PRECAUTIONS, Renal and 4 DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C- 30°C. Protect from excessive heat and moisture.

12 SPECIAL HANDLING INSTRUCTIONS

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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

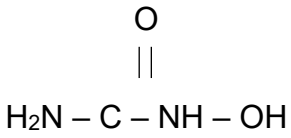
Drug Substance

Proper Name: Hydroxyurea

Chemical Name: 1) carbamyl hydroxylamine
2) hydroxycarbamide

Molecular formula and molecular mass: $CH_4N_2O_2$, 76.05 g/mol

Structural Formula:



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

14 CLINICAL TRIALS

The data on which the indication was originally approved are not available.

14.3 Comparative Bioavailability Studies

A blinded, randomized, two-treatment, two-period, single oral dose (1 x 500 mg), crossover comparative bioavailability study of APO-HYDROXYUREA capsules 500 mg (Apotex Inc.) and HYDREA® capsules 500 mg (Squibb Canada Inc.), was conducted in healthy, adult male subjects under fasting conditions. Comparative bioavailability data from 24 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Hydroxyurea (1 x 500 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**95% Confidence Interval**
AUC_T (mcg·h/mL)	37.1 37.7 (19)	36.4 36.8 (15)	102.0	98.8 – 105.3
AUC_I (mcg·h/mL)	41.6 42.1 (17)	40.8 41.2 (15)	101.9	99.1 – 104.9
C_{max} (mcg/mL)	9.22 9.41 (22)	9.49 9.74 (25)	97.2	88.0 – 107.3
T_{max}[3] (h)	0.74 (36)	0.66 (44)		
$T_{½}$[3] (h)	4.24 (31)	4.44 (33)		

[1] APO-HYDROXYUREA (hydroxyurea) capsules, 500 mg (Apotex Inc.)
[2] HYDREA® (hydroxyurea) capsules, 500 mg (Squibb Canada Inc.)
[3] Expressed as the arithmetic mean (CV %) only

A blinded, randomized, two-treatment, two-period, single oral dose (1 x 500 mg), crossover comparative bioavailability study of APO-HYDROXYUREA capsules 500 mg (Apotex Inc.) and HYDREA® capsules 500 mg (Squibb Canada Inc.), was conducted in healthy, adult male subjects under fed conditions. Comparative bioavailability data from 23 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Hydroxyurea (1 x 500 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**95% Confidence Interval**
AUC_T (mcg·h/mL)	36.0 36.4 (13)	36.2 36.5 (12)	99.4	95.6 – 103.5
AUC_I (mcg·h/mL)	39.6 40.1 (12)	39.7 40.0 (11)	99.8	96.1 – 103.6
C_{max} (mcg/mL)	7.03 7.14 (16)	6.76 6.88 (18)	103.9	97.4 – 110.8
T_{max}[3] (h)	2.42 (29)	2.19 (34)		

Hydroxyurea (1 x 500 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**95% Confidence Interval**
$T_{½}$[3] (h)	3.32 (17)	3.45 (19)		

[1] APO-HYDROXYUREA (hydroxyurea) capsules, 500 mg (Apotex Inc.)
[2] HYDREA® (hydroxyurea) capsules, 500 mg (Squibb Canada Inc.)
[3] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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 - 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.

Reproductive and Developmental Toxicology:

Studies on rats given aqueous solutions of hydroxyurea orally revealed temporarily decreased fertility in male Fo generation rats due to aspermatogenesis. In Fo 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.

Hydroxyurea has been demonstrated to be teratogenic in multiple 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. HYDREA® (Capsule, 500 mg), Submission Control 286140, Product Monograph, CHEPLAPHARM Arzneimittel GmbH. (SEP 17, 2024)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-HYDROXYUREA

Hydroxyurea Capsules

Read this carefully before you start taking **APO-HYDROXYUREA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-HYDROXYUREA.**

What is APO-HYDROXYUREA used for?

APO-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.

How does APO-HYDROXYUREA work?

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

What are the ingredients in APO-HYDROXYUREA?
Medicinal ingredients: Hydroxyurea.

Non-medicinal ingredients: Methylcellulose, stearic acid and talc.

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 ingredients, black iron oxide, potassium hydroxide, propylene glycol, shellac and strong ammonia solution.

APO-HYDROXYUREA comes in the following dosage forms:
Capsules: 500 mg hydroxyurea

Do not use APO-HYDROXYUREA if:

- you have problems with your bone marrow (low blood count, severe anemia).
- you are allergic to hydroxyurea or any other component of this medication.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-HYDROXYUREA. Talk about any health conditions or problems you may have, including if you:

- have problems with your kidneys**.** This is because the dose of APO-HYDROXYUREA may need to be adjusted.
- 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.
- 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).
- recently received or are planning to receive a vaccination. Patients taking APO-HYDROXYUREA should not receive live vaccines.
- 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 receiving interferon treatment.
- have diabetes and are using continuous glucose monitoring systems.

Other warnings you should know about:

High Fever: Tell your healthcare professional 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.

Abnormal test results: APO-HYDROXYUREA can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests. Your healthcare professional will interpret the results**.**

Talk to your healthcare professional if you are using a continuous glucose monitor (CGM) to monitor your blood sugar levels. APO-HYDROXYUREA may give you wrong high blood sugar results. If you take insulin based on these results, you may get low blood sugar levels. Talk to the healthcare professional that prescribed your CGM to see if it is safe to use while you are taking APO-HYDROXYUREA*.* They might monitor your blood sugar levels using a different method.

Tumor Lysis Syndrome (TLS): APO-HYDROXYUREA can cause a serious side effect known as Tumor Lysis Syndrome (TLS). It is a complication of the breakdown of cancer cells. It is serious and can lead to death. Your healthcare professional will monitor you for signs of TLS.

Hemolytic anemia: APO-HYDROXYUREA may cause hemolytic anemia. Hemolytic anemia is a disorder in which the red blood cells are destroyed faster than they can be made. This will be checked by blood tests if you develop persistent anemia.

Interstitial lung disease (ILD): APO-HYDROXYUREA may cause a group of disorders that inflame or scar lung tissue. This is called interstitial lung disease (ILD). Your healthcare professional will monitor you for signs of ILD. These include:

- fever,
- cough,
- shortness of breath and
- other respiratory symptoms.

Cancer: Hydroxyurea , the active ingredient in APO-HYDROXYUREA, may cause cancer and damage to the genetic material in cells (DNA). Protect your skin from sun exposure and regularly examine your skin for unusual spots or moles.

Pregnancy, contraception and breastfeeding:

Female Patients:

- If you are pregnant or planning to become pregnant, there are specific risk you must discuss with your healthcare professional.
- Avoid becoming pregnant while taking APO-HYDROXYUREA. It may harm your unborn child. Use effective contraception methods while taking APO-HYDROXYUREA and for at least 6 months afterwards.
- If you do become pregnant while taking APO-HYDROXYUREA, tell your healthcare professional right away.
- APO-HYDROXYUREA can pass into your breastmilk and harm your baby. Do not breastfeed while you are taking APO-HYDROXYUREA.

Male Patients:

- 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 healthcare professional 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: Until you know how APO-HYDROXYUREA affects you, do not perform tasks which may require special attention. Do not drive, use tools or use machinery if you feel:

- drowsy,
- dizzy,
- weak or
- tired.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

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.
- Live vaccines.
- Radiation therapy.
- Continuous glucose monitoring systems (CGM).

How to take APO-HYDROXYUREA:

- **ALWAYS** wear disposable gloves when handling APO-HYDROXYUREA capsules and bottles containing APO-HYDROXYUREA capsules.
- **Take** APO-HYDROXYUREA exactly as your healthcare professional has indicated.
- Swallow capsules whole.
- Your healthcare professional 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.
- If you cannot swallow APO-HYDROXYUREA capsules whole, empty the contents of the capsules into a glass of water. Drink it right away. Some of the contents of the capsule may not dissolve and float on the surface.
- If any of the contents of APO-HYDROXYUREA capsules are spilled, wipe it up right away with a damp disposable towel.

Usual Adult dose:

The usual dose of APO-HYDROXYUREA will be different for everyone. Your healthcare professional will decide on the right dose for you. Your dose will depend on:

- what APO-HYDROXYUREA is being used to treat,
- your weight, and
- if you are taking other medication.

Your healthcare professional 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:

Some of the signs of an overdose could be:

- 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

If you think you, or a person you are caring for, have taken too much APO-HYDROXYUREA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of this medicine check with your healthcare professional.

What are possible side effects from using APO-HYDROXYUREA?

These are not all the possible side effects you may have when taking APO-HYDROXYUREA. If you experience any side effects not listed here, tell your healthcare professional.

Side effects include:

- rash, redness and ulceration in the face, skin or extremities
- skin or nail changes
- muscle aches and a general, unwell feeling or malaise
- fatigue

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Stomatitis: mouth sores, redness and swelling of the lining of the mouth	✓		
Nausea: feeling the need to vomit	✓		
Vomiting	✓		
Diarrhea	✓		
Constipation	✓		
Cholestasis (decrease in bile flow from the liver): jaundice (yellowing of the skin or whites of eyes), dark urine, light coloured stools			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Hepatitis (inflammation of the liver): Abdominal pain, fatigue, fever, itchiness, light coloured stool, trouble thinking clearly, yellowing of the skin and eyes			✓
UNCOMMON			
Loss of appetite	✓		
Joint pain		✓	
Drowsiness: feeling abnormally sleepy or tired during the day	✓		
Headache: pain and discomfort in the head, scalp, or neck	✓		
Dizziness: feeling faint, woozy, weak or unsteady	✓		
Disorientation: inability to know correct time, place or person		✓	
Convulsions: seizure, spasms, shaking or fits		✓	
Hallucinations: seeing or hearing things that are not there		✓	
Kidney problems: nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, abnormal blood test results, mental status changes (drowsiness, confusion, coma)		✓	
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			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Dyspnea (shortness of breath)			✓
Tumor lysis syndrome (the sudden, rapid death of cancer cells due to the treatment): nausea, shortness of breath, irregular heartbeat, heart rhythm disturbances, lack of urination, clouding of urine, muscle spasms or twitching, tiredness and/or joint pain, severe muscle weakness, and seizures. Metabolic disorders (kidney failure, abnormal heartbeat) and abnormal blood tests due to rapid breakdown of cancer cells.			✓
Cutaneous vasculitis (inflammation of blood vessels of the skin): skin redness/purple 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.		✓	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		✓	
Skin cancer (when cells in the skin become cancerous): skin nodules (e.g. shiny pearly nodules), patches or open sores that do not heal within weeks		✓	
UNKNOWN			
Interstitial lung disease (diseases that inflame or scar lung tissue): shortness of breath when rest			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
that gets worse with exertion, dry cough			
Hemolytic anemia (low number of red blood cells due to their faster breakdown than replacement): pale skin, feeling tired or weak, dizziness, fainting, thirst, rapid breathing		✓	
Systemic lupus (an autoimmune disease that occurs when your body's immune system attacks your own tissues and organs, including your joints, skin, kidneys, blood cells, heart and lungs): fatigue, fever, joint pain, stiffness and swelling, rash on the face hat covers the cheeks and the bridge of the nose or rashes elsewhere on the body, skin lesions, shortness of breath, chest pain, dry eyes, headaches, confusion and memory loss		✓	
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		✓	
Fever: temporary increase in body temperature with sweating, chills, shivering, headache		✓	
Chills		✓	
Leukopenia (decreased white blood cells) –infections, fatigue, fever, aches, pains and flu-like symptoms		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Anemia (decreased number of red blood cells): fatigue, loss of energy, looking pale, shortness of breath, weakness		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.

Storage:
Store at room temperature 15°C – 30°C. Protect from excessive heat and moisture.

Keep out of reach and sight of children.

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 Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); 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.

Last revised: February 28, 2025