DRUG NAME: Hydroxyurea

SYNONYM(S): hydroxycarbamide[1]

COMMON TRADE NAME(S): APO-HYDROXYUREA®, GEN-HYDROXYUREA®, HYDREA®

CLASSIFICATION: alkylating agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Hydroxyurea, a hydroxylated molecule of urea, interferes with the synthesis of DNA via several proposed mechanisms, with little or no effect on RNA or protein synthesis. Hydroxyurea inhibits the conversion of DNA bases by blocking ribonucleotide reductase, thereby preventing conversion of ribonucleotides to deoxyribonucleotides. Hydroxyurea also inhibits the incorporation of thymidine into DNA, and may directly damage DNA.[2,3] Hydroxyurea is cell-cycle specific for the S phase and may hold cells in the G1 phase.[3] Hydroxyurea may also stimulate production of fetal hemoglobin and may have antiviral effects.[2]

PHARMACOKINETICS:

Oral Absorption	>80%,[4] peak levels in 1-4 h	
Distribution	rapidly and widely distributed; concentrates in leukocytes and erythrocytes; found in ascitic fluid	
	cross blood brain barrier?	yes
	volume of distribution[1]	20 L/m^2; approximating total body water
	plasma protein binding[1]	75-80%
Metabolism	50-60% metabolized by liver,[4] small amount degraded by urease in intestinal bacteria	
	active metabolite(s)	no information found
	inactive metabolite(s)	urea,[2] acetohydroxamic acid[3]
Excretion	nonlinear process; saturable hepatic metabolism and renal excretion	
	urine[2-5]	25-80% (50% as unchanged drug, 30% as urea)
	feces	no information found
	terminal half life[4]	3-4 h
	clearance[1]	4.3-5.5 L/h/m^2

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:
*Head and neck cancer
*Leukemia, chronic myelogenous
*Melanoma
*Ovarian cancer

Other uses:
Cervical cancer[2]
Leukemia, acute myeloid[6]
Lung cancer, non-small cell[4]
Myeloproliferative disorders[2]
Uterine cancer[4]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindicated in patients who have a history of hypersensitivity reaction to hydroxyurea, any components of the formulation, or marked bone marrow depression.[3]

Caution: Use of hydroxyurea in combination with antiretroviral agents, particularly didanosine and/or stavudine, is not recommended due to risk of serious toxicities, namely pancreatitis, hepatotoxicity, and peripheral neuropathy; if the combination is used, monitor for toxicities.[3]

Previous or current chemotherapy: increased risk of bone marrow suppression; dose adjustment may be required.[3]

Carcinogenicity: Hydroxyurea is carcinogenic.[2,3]

Mutagenicity: Mutagenic in Ames test and mammalian *in vitro* mutation test. Hydroxyurea is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2]

Fertility: Hydroxyurea should not be used in men contemplating fatherhood.[4] No information found for women.

Pregnancy: FDA Pregnancy Category D.[2,4] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the secretion of hydroxyurea into breast milk.[3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[7] When placebo-controlled trials are available, adverse events are included if the incidence is ≥ 5% higher in the treatment group.

Hydroxyurea is generally well tolerated, serious side effects are rare.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	lupus erythematosus[1]
blood/bone marrow/ febrile neutropenia	***anemia*** (>5%)[8]; seldom seen without a preceding leukopenia ***macrocytosis***[4]; may mask folic acid deficiency megaloblastic erythropoiesis; self-limiting, typically occurs soon after initiating therapy[2]
	hemolysis[2]
	leukopenia (>5%)[8]; onset 24-48 h, nadir 10 days,[4] recovery from myelosuppression is usually rapid when hydroxyurea treatment is interrupted
	thrombocytopenia (1-5%)[8]; onset 7 days, nadir 10 days,[9] recovery from myelosuppression is usually rapid when hydroxyurea treatment is interrupted, seldom seen without a preceding leukopenia
constitutional symptoms	chills
	drowsiness; dose related[2]; incidence (>5%) with large doses[8]
	fever; typically occurs within hours, though 21 days has been reported[1]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	fatigue
dermatology/skin	alopecia (1-5%)[8]; typically occurs after long term use
	miscellaneous dermatological toxicities; see discussion following **Side Effects** table
gastrointestinal	*emetogenic potential: rare*[10]
	anorexia (>5%)[8]
	constipation (1-5%)[8]
	diarrhea (>5%)[8]
	mucositis, stomatitis (1-5%)[8]
	nausea and vomiting (>5%)[8]
	ulcerations of buccal mucosa and GI epithelium with hydroxyurea intoxication,[2] potentiated with radiation therapy[4]
hepatobiliary/pancreas	hepatotoxicity
	pancreatitis
lymphatics	edema[2]
metabolic/laboratory	decreased serum iron[2]
	elevated blood urea nitrogen
	elevated creatinine
	elevated hepatic enzymes[4]
	hyperuricemia (<1%)[8]
neurology	disorientation, hallucinations[4] (<1%)[8]
	dizziness (<1%)[8]
	seizures (<1%)[8]
ocular/visual	blepharitis[1]
pain	headache (<1%)[8]
pulmonary	acute pulmonary reactions; pulmonary infiltrates, fibrosis, dyspnea with or without fever[2]
renal/genitourinary	dysuria (<1%)[8]
	suppressed renal tubular function[2]
secondary malignancy	secondary leukemia[2]; it is unknown if this is secondary to hydroxyurea or underlying disease
	skin cancer

Adapted from standard reference[3] unless specified otherwise.

Dermatological effects: Reports of skin reactions with hydroxyurea include dermopathy, vasculitic toxicities, leg ulcers, and exacerbation of irradiation erythema. Rarely, skin cancers have also occurred.[3]

Hydroxyurea-induced *dermopathy* includes maculopapular rash, atrophy and hyperpigmentation of the skin and nails, peripheral and facial edema, violet papules, and scaly erythematous skin lesions often resembling dermatomyositis.[2,3] Dermatomyositis-like lesions usually occur after several years of treatment, are usually benign,

and are likely due to the chronic cumulative toxicity of hydroxyurea or one of its metabolites.[5] Treatment withdrawal is usually necessary and symptoms may take weeks to months to resolve.[1,5] Nail pigmentation has been reported in up to 5% of patients taking hydroxyurea; pigmentation typically occurs weeks to years after starting therapy.[1,8,11]

Vasculitic toxicities, including vasculitic ulceration and gangrene have been associated with hydroxyurea use, particularly in patients receiving or who have received interferon.[3,12-14] Due to potentially serious clinical outcomes, hydroxyurea should be discontinued if cutaneous vasculitic ulcerations develop.[12] Persons handling hydroxyurea and its packaging are advised to wash their hands after contact.[7]

Hydroxyurea can cause painful *leg ulcers*, often on the malleoli.[2] Leg ulcers often coexist with dermatomyositis-like lesions and may be caused by the same mechanism; mechanical injury, cutaneous atrophy, and poor wound healing may have a role.[5] There is no consistent correlation between dose and duration of hydroxyurea therapy and leg ulcers.[1,11] Ulcers generally improve following discontinuation of therapy[2,11]; recurrence has been reported with reintroduction of hydroxyurea.[14,15]

Hydroxyurea has the potential to enhance *radiation injury* to tissues; it can also induce a recall phenomenon in previously irradiated tissue.[3,8,16] The development of radiation dermatitis may occur weeks to years after radiation. While the exact mechanism is not clearly understood, radiation's effect on the microvasculature, or altered cutaneous immunologic responses have been suggested.[16] Dermatologic manifestations include maculopapular eruptions with erythema, vesicle formation, and desquamation of the skin. Reactions range in intensity from a mild rash to severe skin necrosis. Topical corticosteroids have been used to treat the dermatitis.[16]

Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.[17] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[18]:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 ml/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[19] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminium hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminium hydroxide has been added, discontinue sodium bicarbonate.[20]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
cytarabine[3]	increased cytarabine therapeutic and toxic effects	hydroxyurea depletes deoxycytidine triphosphate resulting in increased uptake of cytarabine, phosphorylation of cytarabine to the active triphoshate, binding to DNA polymerase and subsequent incorporation in to DNA[21]	clinical importance as yet unknown
didanosine (with or without stavudine)[3,4,8,22]	increased risk of hepatotoxicity, hepatic failure, pancreatitis, and neuropathy	unknown	avoid concomitant use[4]; if used monitor for signs and symptoms of hepatotoxicity, pancreatitis, and neuropathy[22]

AGENT	EFFECT	MECHANISM	MANAGEMENT
fluorouracil[9,21]	increased fluorouracil therapeutic and toxic effects	hydroxyurea depletes deoxyuridine monophosphate, leading to greater inhibition of thymidylate synthetase by fluorouracil and subsequent reduced DNA synthesis	clinical importance as yet unknown
triglyceride measurement by glycerol oxidase method[9,23]	false-negative triglyceride measurement	inhibition of glycerol oxidase by hydroxyurea	monitor triglycerides with a different assay

SUPPLY AND STORAGE:

Tablets: Apotex, Bristol-Myers Squibb, and Genpharm supply hydroxyurea as a 500 mg capsule. Selected non-medicinal ingredients in the Bristol-Myers Squibb product: lactose.[3] Store at room temperature and protect from light, excessive heat, and moisture.[3]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BCCA usual dose noted in ***bold, italics***

Oral:

20-30 mg/kg PO once daily[1-3,5]

80 mg/kg PO as a single dose every third day[1-3,5]

up to 12 g/day has been used for blast crisis[1]

- Dose on actual or ideal weight, whichever is less.
- Round dose to the nearest 500 mg.
- Doses can be divided (e.g., BID-QID).
- Administer with food or on an empty stomach.
- Adjust dose according to hematologic response.
- In patients unable to swallow hydroxyurea capsules; the capsules may be emptied into a glass of water and taken immediately. Inert material used as a vehicle in the capsule may not dissolve and may float on the surface.
- Patients and caregivers should be advised to not allow the powder to come in to contact with the skin and mucous membranes and to wash their hands after contact with hydroxyurea and its packaging.

Concurrent radiation:

increased risk of bone marrow suppression[3]; hydroxyurea may potentiate adverse effects usually seen with radiation, namely gastric distress and mucositis[3]; hydroxyurea may cause irradiation erythema in patients who have received radiation[3]; when used with radiation, hydroxyurea should be started at least 7 days before radiation[4]

Dosage in myelosuppression:

modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

BCCA usual dose noted in ***bold, italics***

Dosage in renal failure[4]:

initial dose adjustment may be required; use with caution and monitor hematological parameters[3]; suggested initial dose modification:

Creatinine clearance (mL/min)	Dose
>50	100%
10-50	50%
<10	20%

* e.g., if creatinine clearance = 30 mL/min, give 50% of full dose

Calculated creatinine clearance = $\frac{N^* \times (140 - \text{Age}) \times \text{weight (kg)}}{\text{Serum Creatinine in } \mu\text{mol/L}}$

* For males N = 1.23; for females N=1.04

Dosage in hepatic failure:

monitor hematological parameters[3]

Dosage in dialysis:

hemodialysis: administer dose after dialysis on dialysis days; supplemental dose not necessary[4]

continuous ambulatory peritoneal dialysis: no information found

continuous arteriovenous hemofiltration: dose for creatinine clearance 10-50 mL/min[4]

Children:

safety and effectiveness not established in children[3]; hydroxyurea has been used in pediatric patients[1,9]

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