Drug Monograph

A - Drug Name

hydroxyurea

COMMON TRADE NAME(S): Hydrea®

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B - Mechanism of Action and Pharmacokinetics

Hydroxyurea acts primarily as an inhibitor of ribonucleotide reductase. This leads to the depletion of essential DNA precursors. Repair of DNA damage is also inhibited. Hydroxyurea is cell cycle phase-specific (S-phase) and is a known radiosensitizer, possibly due to G1 arrest.

Absorption	Bioavailability	Oral bioavailability ≥ 80%. Peak levels reached in 1-4 hours after oral dosing. Increasing doses result in a greater than proportional exposure.
	Effects with food	Unknown
Distribution	Distributed throughout body, crosses placenta, found in ascitic fluid. Concentrates in leukocytes and erythrocytes.	
	Cross blood brain barrier?	Yes
	PPB	75-80%
Metabolism	Up to 50% metabolized in liver; a minor pathway involves degradation by urease in intestinal bacteria.	
	Active metabolites	Unknown

	Inactive metabolites	Yes
Elimination	Hepatic and renal; renal is the major route of elimination.	
	Urine	80% within 12 hours
	Half-life	2 to 4.5 hours

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C - Indications and Status

Health Canada Approvals:

- Head and neck cancer (excluding the lip)
- Chronic myelocytic leukemia

Refer to the product monograph for a full list and details of approved indications.

Other Uses:

- Hematological, including:
  - Acute lymphoblastic leukemia
  - Acute myeloid leukemia
  - CMML and myeloproliferative disorders

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Dermatological	Alopecia (rare) (may occur after several years of long-term therapy)	E L
	Dermatomyositis (dermatomyositis-like changes)	E
	Nail disorder (including melanonychia) (atrophy may occur after several years of long-term therapy)	E L

	Radiation recall reaction	I E
	Rash (≥10%) (may be severe)	E L
	Skin hyperpigmentation , atrophy (may occur after several years of long-term therapy)	E L
Gastrointestinal	Anorexia (≥10%)	E
	Constipation	E
	Diarrhea (≥10%)	I
	GI irritation	E
	Mucositis	E
	Nausea, vomiting (≥10%)	I E
General	Chills	E
	Fatigue (≥10%)	E
	Fever (≥10%) (drug-induced)	E
Hematological	Hemolytic anemia (rare)	E
	Myelosuppression (≥10%) (leukopenia most common; rapid recovery after dose interruption)	E
	Other (megaloblastosis)	E
Hepatobiliary	Cholestasis (<10%)	E
	↑ LFTs (<10%) (may be severe)	E
	Pancreatitis (rare, in HIV)	E
Immune	Autoimmune disorder – systemic or cutaneous lupus (rare)	L
Metabolic / Endocrine	Tumor lysis syndrome (rare)	I E
Neoplastic	Secondary malignancy (including skin cancer; rare)	L
Nervous System	Dizziness (rare)	E
	Hallucinations (rare)	E
	Headache (rare)	E
	Peripheral neuropathy (rare, in HIV)	E
	Seizure (rare)	E
Renal	Creatinine increased (uncommon)	E
Respiratory	Pneumonitis (acute; rare)	I
	Pulmonary fibrosis (acute; rare)	I
Urinary	Dysuria (rare)	E
Vascular	Peripheral ischemia (cutaneous ulcers, gangrene; rare)	E

	Vasculitis (cutaneous; rare) (may be severe)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Hydroxyurea has the potential to enhance radiation injury to tissues. While often-called **radiation recall reactions,** the timing of the radiation may be before, concurrent with or even after the administration of hydroxyurea. Recurrent injury to a previously radiated site may occur weeks to months following radiation.

Megaloblastic erythropoiesis, which is self-limiting, is often seen early in the course of hydroxyurea therapy. The macrocytosis is not related to vitamin B12 or folic acid deficiency, but may mask the incidental development of folic acid deficiency; thus, prophylactic administration of folic acid may be warranted.

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.

Drug-induced pyrexia has been reported with hydroxyurea, usually occurring within 6 weeks of initiation and resolving after discontinuation. In some cases, it may present with gastrointestinal, pulmonary, musculoskeletal, hepatobiliary, dermatological or cardiovascular effects. Fever may recur within 24 hours of re-challenge.

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

Hepatitis and/or **cholestasis** has been commonly described and may be severe. **Fatal hepatic events** were reported during post-marketing in HIV-infected patients treated with hydroxyurea and other antiretroviral agents.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Severe anemia must be corrected prior to initiation of treatment with hydroxyurea.

Patients at risk of tumour lysis syndrome (i.e. high tumour burden) should have appropriate prophylaxis and be monitored closely.

Skin cancer has been reported in patients on long-term hydroxyurea. Patients should be advised to protect skin from sun exposure.

Adults:

Dosing should be based on patient's actual or ideal weight, whichever is less.

CML:

- Daily: 20-30 mg/kg po, adjusted to white cell count

Head and neck cancer:

- Refer to product monograph.

Dosage with Toxicity:

Doses should be modified according to the protocol by which patient is being treated; if no guidelines available, refer to Dosage Modification for Hematologic and Non-Hematologic Toxicities.

Toxicity	Action
Mild to moderate anemia	Transfuse if symptomatic; do not interrupt.
Worsening or persistent anemia	Consider hold and evaluate for hemolysis. Discontinue if hemolytic anemia is confirmed.
Severe mucositis or gastric distress (e.g., nausea, vomiting, and anorexia)	Hold until ≤ grade 1.
Vasculitis	Discontinue.
Hepatitis or cholestasis	Discontinue.
Interstitial lung disease	Discontinue. Manage with corticosteroids.

Dosage with Hepatic Impairment:

No data available; close hematologic monitoring recommended.

Dosage with Renal Impairment:

Hydroxyurea should be used with caution in patents with renal impairment; close hematologic monitoring is recommended. In patients with CrCl < 60 mL/min (or ESRD), there was an approximate 64% increase in mean hydroxyurea exposure.

Creatinine Clearance (mL/min)	Starting Dose (% usual dose)
> 60	100%
10-60	50%
<10	20%* or Discontinue

*Give hydroxyurea after dialysis on dialysis days.

Dosage in the elderly:

May be more sensitive to toxic effects. Consider dosage adjustment.

Children:

Safety and efficacy have not been established.

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F - Administration Guidelines

- To minimize the risk of exposure, always wash hands before and after handling hydroxyurea. Always wear impervious gloves when handling hydroxyurea capsules or packaging.
- If patient is unable to swallow capsules, capsule contents may be emptied into a glass of water and taken immediately. Some inert material used as vehicle in the capsule may not dissolve and float on the surface.
- Patients should not allow the drug powder to come in contact with their skin or mucous membranes and avoid inhaling the powder when opening the capsules.
- Store at room temperature (15 - 30°C) and protect from excessive heat and moisture.

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G - Special Precautions

Contraindications:

- Patients with marked myelosuppression (WBC < 2.5 x 10^9/L or platelets < 100 x 10^9/L), or severe anemia
- Patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component in its formulation

Other Warnings/Precautions:

- Avoid the use of live vaccines.
- Patient's antibody response to inactivated vaccines may be suboptimal.
- Avoid combination of hydroxyurea with antiretrovirals, particularly didanosine and/or stavudine, due to risk of serious toxicities. (Refer to interactions.)
- Use with caution in patients who have recently received extensive radiotherapy or chemotherapy.
- Exercise caution when driving or using machinery since hydroxyurea may cause drowsiness or other neurologic effects.
- Some brands of hydroxyurea contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Fetotoxicity: Yes
- Teratogenicity: Yes
- Genotoxicity: Yes
- Mutagenicity: Yes
  Hydroxyurea is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose (for females) and **12 months** after the last dose (for males).
- Excretion into breast milk: Yes
  Breastfeeding is not recommended.
- Fertility effects: Probable
  Male fertility may be affected, but may be reversible. Sperm banking should be offered for males due to effects on fertility.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Cytarabine	↑ Cytarabine toxicity	Unknown	Caution
Didanosine +/- stavudine, other antiretrovirals	↑ incidence of pancreatitis, liver failure and neurotoxicity	Unknown	Avoid
Myelosuppressive agents or radiation therapy	Can potentiate bone marrow depression	Additive	Caution
Uricosuric agents	↓ uricosuric effect	Hydroxyurea may ↑ uric acid levels	Adjust dose of uricosuric agents as necessary.
In vitro enzymatic assays	↑ urea, uric acid and lactic acid levels	Analytical interference by hydroxyurea	Caution; unknown relevance

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and as clinically indicated
Renal function tests	Baseline and as clinically indicated
Liver function tests	Baseline and as clinically indicated
Clinical assessment of fever, infection, bleeding, TLS, secondary malignancies (including skin), respiratory, skin, gastrointestinal, and neurologic effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Serum folic acid	Baseline and as clinically indicated

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- hydroxyurea ()

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K - References

Antonioli E, et al. Hydroxyurea-related toxicity in 3,411 patients with Ph'-negative MPN. Am J Hematol. 2012 May;87(5):552-4.

Belt RJ, Haas CD, Kennedy J, et al. Studies of hydroxyurea administered by continuous infusion: toxicity, pharmacokinetics, and cell synchronization. Cancer 1980;46:455-62.

Golightly L, Teitelbaum I, Kizer TH, et al. (Eds). Dosage adjustment of medications eliminated by the kidneys, Springer, New York 2013.

Hydroxyurea monograph. Cancer Drug Manual. British Columbia Cancer Agency (BCCA). Accessed Jan 4, 2021.

Hydroxyurea: eDrugDex, Micromedex Healthcare Series.

Mason WP, Gentili F, Macdonald DR, et al. Stabilization of disease progression by hydroxyurea in patients with recurrent or unresectable meningioma. J Neurosurg 2002; 97: 341–6.

Product Monograph: Hydrea® (hydroxyurea). Bristol-Myers Squibb Canada, November 2022.

Rodriguez GI, Kuhm JG, Weiss, GR, et al. A bioavailability and pharmacokinetic study of oral and intravenous hydroxyurea. Blood 1998:91:533-41.

Summary of Product Characteristics: hydroxyurea (Hydrea®). Bristol-Myers Squibb Pharmaceuticals Ltd. (UK), July 2019.

March 2023 Updated Adverse effects, Dosing (including dose modification), and Monitoring sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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