HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HYDROXYUREA Capsules safely and effectively. See full prescribing information for HYDROXYUREA Capsules.

HYDROXYUREA capsules, USP, for oral use
Initial U.S. Approval: 1967

RECENT MAJOR CHANGES
Indications and Usage, melanoma (1) Removed 7/2015 (1)
Carcinoma of the ovary (1) Removed 7/2015 (1)
Dosage and Administration (2) 7/2015
Warnings and Precautions, Embryo-Fetal Toxicity (5.3) 3/2016

INDICATIONS AND USAGE
Hydroxyurea capsules, USP is an antimitabolite indicated for the treatment of:
• Resistant chronic myeloid leukemia. (1)
• Locally advanced squamous cell carcinomas of the head and neck, (excluding lip) in combination with concurrent chemoradiation. (1)

Dosage and Administration
Individualize treatment based on tumor type, disease state, response to treatment, patient risk factors, and current clinical practice standards. (2.1)
Renal impairment: Reduce the dose of hydroxyurea by 50% in patients with creatinine clearance less than 60 mL/min. (2.3, 8.6, 12.3)

DOSAGE FORMS AND STRENGTHS
• Capsules: 500 mg (3)

CONTRAINDICATIONS
• In patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation. (4)

WARNINGS AND PRECAUTIONS
• Myelosuppression: Do not give if bone marrow function is markedly depressed. Monitor hematologic labs and interrupt, reduce dose as appropriate. (5.1)
• Malignancies: Advise protection from sun exposure and monitor for secondary malignancies. (5.2)
• Embryo-Fetal Toxicity. Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.3, 8.1, 8.3)
• Vasculitic toxicities: Discontinue hydroxyurea and initiate treatment if this occurs. (5.4)
• Live Vaccinations: Avoid live vaccine use in a patient taking hydroxyurea capsules. (5.5)
• Risks with concomitant use of antiretroviral drugs: Pancreatitis, hepatotoxicity, and neuropathy have occurred. Monitor for signs and symptoms in patients with HIV infection using antiretroviral drugs; discontinue hydroxyurea capsules, and discontinue antiretroviral drugs. (5.6)
• Radiation recall: Monitor for skin erythema in patients who previously received radiation and manage symptomatically. (5.7)

ADVERSE REACTIONS
Most common adverse reactions (50%) are hematologic, gastrointestinal, and dermatologic. (5.2)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

IN USE IN SPECIFIC POPULATIONS

Lactation Hydroxyurea is excreted in human milk. Discontinue breastfeeding during treatment with hydroxyurea capsules. (8.2)

Geriatric Use Care should be taken in dose selection and may require a lower dose regimen and monitoring of renal function. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2016

1 USE IN SPECIFIC POPULATIONS

1.1 Increased Toxicity with Concomitant Use of Antiretroviral Drugs

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

Recommended Hydroxyurea capsules initial dose: 15 mg/kg daily

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Recommended Hydroxyurea capsules initial dose (mg/kg daily)</th>
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<tbody>
<tr>
<td>≥ 60</td>
<td>15</td>
</tr>
<tr>
<td>&lt; 60 or ESRD*</td>
<td>7.5</td>
</tr>
</tbody>
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* On dialysis days, administer hydroxyurea capsules to patients following hemodialysis.

Close monitoring of hematologic parameters is advised in these patients.

2.2 Dose Modifications for Toxicity

Use the following to follow and reduce the dose or discontinue hydroxyurea accordingly:
• Myelosuppression [see Warnings and Precautions (5.1)]
• Cutaneous vasculitis [see Warnings and Precautions (5.4)]

2.3 Dose Modifications for Renal Impairment

Reduce the dose of hydroxyurea capsules by 50% in patients with measured creatinine clearance of less than 60 mL/min or with end-stage renal disease (ESRD) [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

2.4 Dose Modifications for Other toxics

3 CONTRAINDICATIONS

Hydroxyurea capsules are contraindicated in patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Hydroxyurea causes severe myelosuppression. Treatment with hydroxyurea can be considered if bone marrow function is markedly depressed. Bone marrow suppression may occur, and leukopenia is generally its first and most common manifestation. Thrombocytopenia and anemia occur less often and are seldom seen without a preceding leukopenia. Bone marrow depression is more likely in patients who have previously received radiotherapy or cytotoxic cancer chemotherapy agents; use hydroxyurea cautiously in such patients.

Evaluate hematologic status prior to and during treatment with hydroxyurea capsules. Provide supportive care and modify dose or discontinue hydroxyurea as needed. Recovery from myelosuppression is usually rapid when treatment is interrupted.

5.2 Malignancies

Hydroxyurea is a human carcinogen. In patients receiving long-term hydroxyurea for myeloproliferative disorders, secondary leukemia has been reported. Skin cancer has also been reported in patients receiving long-term hydroxyurea. Advise protection from sun exposure and monitor for the development of secondary malignancies.

5.3 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, hydroxyurea can cause fetal harm when administered to a pregnant woman. Hydroxyurea was embryotoxic and teratogenic in rabbits at doses of 0.8 times and 0.3 times, respectively, the maximum recommended human dose on a mg/m2 basis. Advise pregnant women of the potential risk to a fetus [see Use in Specific Populations (8.1)].

Advise females of reproductive potential to use effective contraception during and after treatment with hydroxyurea capsules for at least 6 months after therapy. Advise males of reproductive potential to use effective contraception during and after treatment with hydroxyurea capsules for at least 1 year after therapy [see Use in Specific Populations (8.1, 8.3)].

5.4 Vasculitic Toxicities

Cutaneous vasculitic toxicities, including vasculitic ulcers 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. If cutaneous vasculitic ulcers occur, institute treatment and discontinue hydroxyurea capsules.

5.5 Live Vaccinations

Avoid use of live vaccine in patients taking hydroxyurea capsules. Concomitant use of hydroxyurea capsules with a live virus vaccine may potentiate the replication of the virus and/or may increase the adverse reaction of the vaccine because normal defense mechanisms may be suppressed by hydroxyurea capsules. Vaccination with live vaccines in a patient receiving hydroxyurea capsules may result in severe infection. Patient’s antibody response to vaccines may be decreased. Consider consultation with a vaccinologist.

5.6 Risks with Concomitant Use of Antiretroviral Drugs

Pancreatitis, hepatotoxicity, and peripheral neuropathy have occurred when hydroxyurea was administered concomitantly with antiretroviral drugs, including didanosine and stavudine [see Drug Interactions (7.1)].

5.7 Radiation Recall

Patients who have received irradiation therapy in the past may have an exacerbation of postirradiation syndrome. Monitor for skin erythema in patients who previously received radiation and manage symptomatically.

5.8 Macrocytosis

Hydroxyurea capsules may cause macrocytosis, which is self-limiting, and is often seen early in the course of treatment. The morphologic change resembles pernicious anemia, but is not related to vitamin B12 or folate deficiency. This may mask the diagnosis of pernicious anemia. Prophylactic administration of folic acid is recommended.

6 ADVERSE REACTIONS

The following adverse reactions are described in detail in other labeling sections:

• Myelosuppression [see Warnings and Precautions (5.1)]
• Malignancies [see Warnings and Precautions (5.2)]
• Embryo-fetal toxicity [see Warnings and Precautions (5.3)]
• Vasculitic toxicities [see Warnings and Precautions (5.4)]
• Risks with concomitant use of antiretroviral drugs [see Warnings and Precautions (5.6)]
• Radiation recall [see Warnings and Precautions (5.7)]
• Macrocytosis [see Warnings and Precautions (5.8)]

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of hydroxyurea capsules. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

• Reproductive System and Breast disorders: azospermia, and oligospermia
• Gastrointestinal disorders: stomatitis, nausea, vomiting, diarrhea, and constipation
• Mental and Nervous disorders: anorexia, tumor lysis syndrome
• Skin and subcutaneous tissue disorders: maculopapular rash, skin ulceration, dermatomyositis-like skin changes, peripheral and facial erythema, hyperpigmentation, atrophy of skin and nails, scaling, violet papules, and alopecia
• Renal and urinary disorders: dysuria, elevations in serum uric acid, blood urea nitrogen (BUN), and creatinine
• Nervous system disorders: headache, dizziness, drowsiness, disorientation, hallucinations, and convulsions
• General disorders: fever, chills, malaise, edema, and anemia
• Hematopoietic disorders: elevation of hepatic enzymes, cholestatics, and hepatitis
• Respiratory disorders: diffuse pulmonary infiltrates, dyspnea, and pulmonary fibrosis

Adverse reactions observed with combined hydroxyurea and irradiation therapy are similar to those reported with the use of hydroxyurea or radiation treatment alone. These effects primarily include bone marrow depression (anemia and leukopenia), gastrointestinal, and skin toxicity. Almost all patients receiving an adequate course of combined hydroxyurea and irradiation therapy will demonstrate concurrent leukopenia. Platelet depression (<100,000 cells/mm3) has occurred in patients treated with this combination, but leukopenia is not a marked leukopenia. Hydroxyurea capsules may potentiate some adverse reactions usually seen with irradiation alone, such as gastric distress and mucositis.

7 DRUG INTERACTIONS

7.1 Increased Toxicity with Concomitant Use of Antiretroviral Drugs

Pancreatitis is uncommon in patients with HIV infection during therapy with hydroxyurea and didanosine, with or without stavudine, fatal and nonfatal pancreatitis have occurred. Hydroxyurea is not indicated for the treatment of HIV infection; however, if patients with HIV infection are treated with hydroxyurea,
in and in particular, in combination with didanosine and stavudine, close monitoring for signs and symptoms of pancreatitis is recommended. Permanently discontinue therapy with hydroxyurea in patients who develop signs and symptoms of pancreatitis.

Hepatotoxicity

Hepatotoxicity and hepatic failure resulting in death have been reported during postmarketing surveillance in patients with HIV infection treated with hydroxyurea and other antiretroviral drugs. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine, and stavudine. Avoid this combination.

Peripheral Neuropathy

Peripheral neuropathy, which was severe in some cases, has been reported in patients with HIV infection receiving hydroxyurea in combination with didanosine and stavudine, including didanosine, with or without stavudine.

7.2 Test Interference

Interference with Uric Acid, Urea, or Lactic Acid Assays

Studies have shown that there is an analytical interference of hydroxyurea with the determination of urea, uric acid, and lactate dehydrogenase used in the determination of urea, uric acid, and lactate, rendering falsely elevated results of these in patients treated with hydroxyurea.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Hydroxyurea capsules can cause fetal harm based on findings from animal reproduction studies and human data. The mechanism of action (see Clinical Pharmacology (12.1)) suggests a potential mechanism of action (see Clinical Pharmacology (12.1)) that has been observed in animal studies. In animal reproduction studies, administration of hydroxyurea to pregnant rats and rabbits caused growth retardation and developmental delays. Hydroxyurea crosses the placenta.

Clinical Pharmacology

Metabolism

Hydroxyurea is a white to off-white crystalline powder. It is hygroscopic and freely soluble in water, but practically insoluble in alcohol. The empirical formula is \( \text{C}_4\text{H}_7\text{N}_2\text{O}_2 \) and it has a molecular weight of 76.05. Its structural formula is:

\[
\text{H}_2\text{N} - \text{C} \quad \text{—} \quad \text{NH} - \text{OH}
\]

Clinical Pharmacology

12.1 Mechanism of Action

The precise mechanism by which hydroxyurea produces its antineoplastic effects cannot be presented with any degree of certainty. However, it is reported that a number of studies in tissue culture in rats and humans lend support to the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, with resulting cell cycle arrest and clastogenic effects.

Three mechanisms of action have been postulated for the increased effectiveness of concomitant use of hydroxyurea therapy with irradiation on squamous cell epidermoid carcinomas of the head and neck. In in vitro studies utilizing Chinese hamster cell lines, it has been shown that hydroxyurea is clastogenic in vivo (1) is lethal to normally radioresistant S-stage cells, and (2) holds other malignant cells in the G1- or DNA synthesis stage whereby 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, induces the normal repair process of cells damaged but not killed by irradiation, thereby decreasing their survival rate; RNA and protein synthesis have been shown to be reduced by hydroxyurea and this reduction was increased by the combination of irradiation and hydroxyurea.

12.3 Pharmacokinetics

Absorption

Following oral administration of hydroxyurea capsules, hydroxyurea reaches peak plasma concentrations in 1 to 4 hours. Mean peak plasma concentrations and AUCs increase more than proportionally with increasing doses. There are no data on the effect of food on the absorption of hydroxyurea.

Distribution

Hydroxyurea distributes throughout the body with a volume of distribution approximating total body water. Hydroxyurea concentrates in leucocytes and erythrocytes.

Metabolism

Up to 60% of an oral dose undergoes conversion through saturable hepatic metabolism and a minor pathway of degradation by urease found in intestinal bacteria.

Excretion

In patients with sickle cell anemia, the mean cumulative urinary recovery of hydroxyurea was about 40% of the administered dose.

10 OVERDOSAGE

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

11 DESCRIPTION

Hydroxyurea Capsules, USP are an antineoplastic agent available for oral use as capsules containing 500 mg hydroxyurea. Inactive ingredients include colloidial silicon dioxide, colorants (D&C Yellow No. 10, FD&C Blue No. 1 and FD&C Red No. 40), gelatin, magnesium stearate and titanium dioxide. Impinging ink constituents: D&C Yellow No. 10 Alumina Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, pharmaceutical glaze, phenylalanine, polyethylene glycol, polychlorohydroxypropylsodium, hydroxide, synthetic black iron oxide and titanium dioxide.

Hydroxyurea is a white to off-white crystalline powder. It is hygroscopic and freely soluble in water, but practically insoluble in alcohol. Its empirical formula is

\[ \text{H}_2\text{N} - \text{C} \quad \text{—} \quad \text{NH} - \text{OH} \]

12 CLINICAL PHARMACOLOGY

8.7 Hepatic Impairment

There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

References