

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HYDREA safely and effectively. See full prescribing information for HYDREA.

HYDREA (hydroxyurea) capsules, for oral use
Initial U.S. Approval: 1967

-----RECENT MAJOR CHANGES-----

| | |
|---|----------------|
| Indications and Usage, melanoma (1) | Removed 7/2015 |
| Indications and Usage, carcinoma of the ovary (1) | Removed 7/2015 |
| Dosage and Administration (2) | 7/2015 |
| Warnings and Precautions, Embryo-Fetal Toxicity (5.3) | xx/201x |
| Warnings and Precautions, Live Vaccinations (5.5) | xx/201x |

-----INDICATIONS AND USAGE-----

HYDREA is an antimetabolite 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 HYDREA 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 hematology 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 HYDREA and initiate treatment if this occurs. (5.4)¹
- Live Vaccinations: Avoid live vaccine use in a patient taking HYDREA. (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 HYDREA, and implement treatment. (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 (≥30%) are hematological, gastrointestinal symptoms, and anorexia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

Antiretroviral drugs (7.1)

-----USE IN SPECIFIC POPULATIONS-----

- *Lactation* Hydroxyurea is excreted in human milk. Discontinue breastfeeding during treatment with HYDREA. (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: 03/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HYDREA is indicated for the treatment of:

- Resistant chronic myeloid leukemia.
- Locally advanced squamous cell carcinomas of the head and neck (excluding the lip) in combination with chemoradiation.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

HYDREA is used alone or in conjunction with other antitumor agents or radiation therapy to treat neoplastic diseases. Individualize treatment based on tumor type, disease state, response to treatment, patient risk factors, and current clinical practice standards.

Base all dosage on the patient's actual or ideal weight, whichever is less.

HYDREA is a cytotoxic drug. Follow applicable special handling and disposal procedures [see *References (15)*].

Prophylactic administration of folic acid is recommended [see *Warnings and Precautions (5.7)*].

2.2 Dose Modifications for Toxicity

Monitor for the following and reduce the dose or discontinue HYDREA accordingly:

- Myelosuppression [see *Warnings and Precautions (5.1)*]
- Cutaneous vasculitis [see *Warnings and Precautions (5.4)*]

Monitor blood counts at least once a week during HYDREA therapy. Severe anemia must be corrected before initiating therapy with HYDREA. Consider dose modifications for other toxicities.

2.3 Dose Modifications for Renal Impairment

Reduce the dose of HYDREA 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)*].

| Creatinine Clearance (mL/min) | Recommended HYDREA Initial Dose (mg/kg daily) |
|----------------------------------|--|
| ≥60 | 15 |
| <60 or ESRD* | 7.5 |

* On dialysis days, administer HYDREA to patients following hemodialysis.

Close monitoring of hematologic parameters is advised in these patients.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 500 mg opaque green cap and opaque pink body imprinted with “HYDREA” and “830.”

4 CONTRAINDICATIONS

HYDREA is 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 should not be initiated 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 chemotherapeutic agents; use hydroxyurea cautiously in such patients.

Evaluate hematologic status prior to and during treatment with HYDREA. Provide supportive care and modify dose or discontinue HYDREA as needed. Recovery from myelosuppression is usually rapid when therapy 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, HYDREA can cause fetal harm when administered to a pregnant woman.² Hydroxyurea was embryotoxic and teratogenic in rats and rabbits at doses 0.8 times and 0.3 times, respectively, the maximum recommended human daily dose on a mg/m² basis. Advise pregnant women of the potential risk to a fetus [*see Use in Specific Populations (8.1)*].³

Advise females of reproductive potential to use effective contraception during and after treatment with HYDREA for at least 6 months after therapy. Advise males of reproductive potential to use effective contraception during and after treatment with HYDREA for at least 1 year after therapy [*see Use in Specific Populations (8.1, 8.3)*].^{4,5}

5.4 Vasculitic Toxicities

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. If cutaneous vasculitic ulcers occur, institute treatment and discontinue HYDREA.

5.5 Live Vaccinations

Avoid use of live vaccine in patients taking HYDREA. Concomitant use of HYDREA 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 HYDREA. Vaccination with live vaccines in a patient receiving HYDREA may result in severe infection. Patient's antibody response to vaccines may be decreased. Consider consultation with a specialist.

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 erythema. Monitor for skin erythema in patients who previously received radiation and manage symptomatically.

5.8 Macrocytosis

HYDREA 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 folic acid 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 HYDREA. 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:* azoospermia, and oligospermia **Error! Bookmark not defined.**
- *Gastrointestinal disorders:* stomatitis, nausea, vomiting, diarrhea, and constipation
- *Metabolism and Nutrition disorders:* anorexia, tumor lysis syndrome^{6,7}
- *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 levels
- *Nervous system disorders:* headache, dizziness, drowsiness, disorientation, hallucinations, and convulsions
- *General Disorders:* fever, chills, malaise, edema, and asthenia
- *Hepatobiliary disorders:* elevation of hepatic enzymes, cholestasis, and hepatitis⁸
- *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), gastric irritation, and mucositis. 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 the presence of marked leukopenia. HYDREA 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

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, and in particular, in combination with didanosine and/or 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 antiretroviral drugs, 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 enzymes (urease, uricase, and lactate dehydrogenase) used in the determination of urea, uric acid, and lactic acid, rendering falsely elevated results of these in patients treated with hydroxyurea.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy⁹

Risk Summary

HYDREA can cause fetal harm based on findings from animal studies and the drug's mechanism of action [see *Clinical Pharmacology (12.1)*]. There are no data with HYDREA use in pregnant women to inform a drug-associated risk. In animal reproduction studies, administration of hydroxyurea to pregnant rats and rabbits during organogenesis produced embryotoxic and teratogenic effects at doses 0.8 times and 0.3 times, respectively, the maximum recommended human daily dose on a mg/m^2 basis (see *Data*). Advise women of the potential risk to a fetus and to avoid becoming pregnant while being treated with HYDREA.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Data

Animal Data

Hydroxyurea has been demonstrated to be a potent teratogen in a wide variety of animal models, including mice, hamsters, cats, miniature swine, dogs, and monkeys at doses within 1-fold of the human dose given on a mg/m^2 basis. Hydroxyurea is embryotoxic and causes fetal malformations (partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae) at 180 $\text{mg}/\text{kg}/\text{day}$ (about 0.8 times the maximum

recommended human daily dose on a mg/m² basis) in rats and at 30 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m² basis) in rabbits. Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. Hydroxyurea crosses the placenta. Single doses of ≥375 mg/kg (about 1.7 times the maximum recommended human daily dose on a mg/m² basis) to rats caused growth retardation and impaired learning ability.

8.2 Lactation

Risk Summary

Hydroxyurea is excreted in human milk. Because of the potential for serious adverse reactions in a breastfed infant from hydroxyurea, including carcinogenicity, discontinue breastfeeding during treatment with HYDREA.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating HYDREA therapy.

Contraception

Females

HYDREA can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during and after treatment with HYDREA for at least 6 months after therapy. Advise females to immediately report pregnancy.

Males

HYDREA may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during and after treatment with HYDREA for at least 1 year after therapy [*see Nonclinical Toxicology (13.1)*].

Infertility

Males

Based on findings in animals and humans, male fertility may be compromised by treatment with HYDREA. Azoospermia or oligospermia, sometimes reversible, has been observed in men. Inform male patients about the possibility of sperm conservation before the start of therapy [*see Adverse Reactions (6) and Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen. Hydroxyurea is excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see *Dosage and Administration (2.3)*].

8.6 Renal Impairment

The exposure to hydroxyurea is higher in patients with creatinine clearance of less than 60 mL/min or in patients with end-stage renal disease (ESRD). Reduce dosage and closely monitor the hematologic parameters when HYDREA is to be administered to these patients [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*].

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.

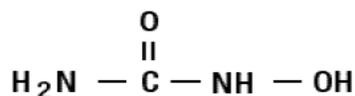
10 OVERDOSAGE

Acute mucocutaneous toxicity has been reported in patients receiving hydroxyurea at dosages 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

HYDREA (hydroxyurea capsules, USP) is an antimetabolite available for oral use as capsules containing 500 mg hydroxyurea. Inactive ingredients include citric acid, colorants (D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red No. 40, and D&C Red No. 28), gelatin, lactose, magnesium stearate, sodium phosphate, 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. The empirical formula is $\text{CH}_4\text{N}_2\text{O}_2$ and it has a molecular weight of 76.05. Its structural formula is¹⁰:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which hydroxyurea produces its antineoplastic effects cannot, at present, be described. However, the reports of various 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, without interfering with the synthesis of ribonucleic acid or of protein. This hypothesis explains why, under certain conditions, hydroxyurea may induce teratogenic 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 vitro* studies utilizing Chinese hamster cells suggest that hydroxyurea (1) is lethal to normally radioresistant S-stage cells, and (2) 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; RNA and protein syntheses have shown no alteration.

12.3 Pharmacokinetics

Absorption

Following oral administration of HYDREA, hydroxyurea reaches peak plasma concentrations in 1 to 4 hours. Mean peak plasma concentrations and AUCs increase more than proportionally with increase of dose.

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 leukocytes 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.

Specific Populations

Renal Impairment

The effect of renal impairment on the pharmacokinetics of hydroxyurea was assessed in adult patients with sickle cell disease and renal impairment. Patients with normal renal function (creatinine clearance [CrCl] >80 mL/min), mild (CrCl 50-80 mL/min), moderate (CrCl = 30-50 mL/min), or severe (<30 mL/min) renal impairment received a single oral dose of 15 mg/kg hydroxyurea. Patients with 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. The exposure to hydroxyurea (mean AUC) in patients with CrCl <60 mL/min and those with ESRD was 64% higher than in patients with normal renal function (CrCl >60 mL/min). Reduce the dose of HYDREA when it is administered to patients with creatinine clearance of <60 mL/min or with ESRD following hemodialysis [see *Dosage and Administration (2.3) and Use in Specific Populations (8.6)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Conventional long-term studies to evaluate the carcinogenic potential of hydroxyurea have not been performed. However, intraperitoneal administration of 125 to 250 mg/kg hydroxyurea (about 0.6-1.2 times the maximum recommended human oral daily dose on a mg/m² basis) thrice weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to control. Hydroxyurea is mutagenic *in vitro* to bacteria, fungi, protozoa, and mammalian cells. Hydroxyurea is clastogenic *in vitro* (hamster cells, human lymphoblasts) and *in vivo* (SCE assay in rodents, mouse micronucleus assay). Hydroxyurea causes the transformation of rodent embryo cells to a tumorigenic phenotype.

Hydroxyurea administered to male rats at 60 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m² basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.¹¹

15 REFERENCES

OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

HYDREA[®] (hydroxyurea capsules, USP) is supplied as 500 mg capsules in HDPE bottles with a plastic safety screw cap. Each bottle contains 100 capsules. The cap is opaque green and the body is opaque pink. The capsules are imprinted on both sections with “HYDREA” and “830” in black ink (NDC 0003-0830-50).

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature]. Keep tightly closed.

16.3 Handling and Disposal

HYDREA is a cytotoxic drug. Follow applicable special handling and disposal procedures [*see References (15)*].

To decrease the risk of contact, advise caregivers to wear disposable gloves when handling HYDREA or bottles containing HYDREA. Wash hands with soap and water before and after contact with the bottle or capsules when handling HYDREA. Do not open HYDREA capsules. Avoid exposure to crushed or opened capsules. If contact with crushed or opened capsules occurs on the skin, wash affected area immediately and thoroughly with soap and water. If contact with crushed or opened capsules occurs on the eye(s), the affected area should be flushed thoroughly with water or isotonic eyewash designated for that purpose for at least 15 minutes. If the powder from the capsule is spilled, immediately wipe it up with a damp disposable towel and discard in a closed container, such as a plastic bag; as should the empty capsules. The spill areas should then be cleaned three times using a detergent solution followed by clean water. Keep the medication away from children and pets. Contact your doctor for instructions on how to dispose of outdated capsules.

17 PATIENT COUNSELING INFORMATION

- There is a risk of myelosuppression. Monitoring blood counts weekly throughout the duration of therapy should be emphasized to patients taking HYDREA [*see Warnings and Precautions (5.1)*]. Advise patients to report signs and symptoms of infection or bleeding immediately.
- Advise patients that there is a risk of cutaneous vasculitic toxicities and secondary malignancies including leukemia and skin cancers [*see Warnings and Precautions (5.2, 5.4)*].
- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy. Advise females and males of reproductive potential to use contraception during and after treatment with HYDREA [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)*].
- Advise patients to inform their healthcare provider if they have received or are planning to receive vaccinations while taking HYDREA as this may result in a severe infection [*see Warnings and Precautions (5.5)*].¹²
- Advise females to discontinue breastfeeding during treatment with HYDREA [*see Use in Specific Populations (8.3)*].
- Patients with HIV infection should contact their physician for signs and symptoms of pancreatitis, hepatic events, and peripheral neuropathy [*see Warnings and Precautions (5.6)*].

- Postirradiation erythema can occur in patients who have received previous irradiation therapy [see *Warnings and Precautions (5.7)*].

Manufactured for:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

Product of Italy

[print code]

Revised: March 2016

ANNOTATIONS

- ¹ Updated to align with DROXIA USPI and language in W&P, Section 5.4.
- ² Removed this text since it is duplicative. Text is already in section 8.1 Pregnancy, animal data.
- ³ Added cross reference
- ⁴ For readability, separated this paragraph since it discusses reproductive potential & contraception. The first paragraph discusses the risk to the fetus.
- ⁵ Removed this cross-reference as the preceding paragraph applies to pregnancy not lactation. Also, lactation is now 8.2 according to PLLR.
- ⁶ “Anorexia” moved to this more relevant SOC according to MedDRA version 17.0.
- ⁷ Hydroxyurea oral formulations. Module 2.5. Clinical overview for tumor lysis syndrome label update. 30 Jun2014. BMS Document Control Number 930081588.
- ⁸ Hydroxyurea, Module 2.5 Clinical Overview for Label Update on Hepatitis and Cholestasis. 03 April 2013. BMS Document Control Number 930069149.
- ⁹ Updated Pregnancy and lactation sections to comply with PLLR.
- ¹⁰ Hydroxyurea. United States Pharmacopeia (USP) Monograph. August 2015; 38: 3811-3812.
- ¹¹ Added cross-reference to Section 5.3.
- ¹² Added to align with text in Full Prescribing Information, Section 5.5.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DROXIA safely and effectively. See full prescribing information for DROXIA.

DROXIA (hydroxyurea) capsules, for oral use
Initial U.S. Approval: 1967

WARNING: MYELOSUPPRESSION AND MALIGNANCIES

See full prescribing information for complete boxed warning.

Myelosuppression: DROXIA may cause severe myelosuppression. Do not give if bone marrow function is markedly depressed. Monitor blood counts at baseline and throughout treatment. Interrupt treatment and reduce dose as necessary. (5.1)

Malignancies: Hydroxyurea is carcinogenic. Advise sun protection and monitor patients for malignancies. (5.2)

RECENT MAJOR CHANGES

Warnings and Precautions, Embryo-Fetal Toxicity (5.3) xx/201x
Warnings and Precautions, Live Vaccinations (5.5) xx/201x

INDICATIONS AND USAGE

DROXIA is an antimetabolite indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in patients with sickle cell anemia with recurrent moderate to severe painful crises. (1)

DOSAGE AND ADMINISTRATION

- Initial dose: 15 mg/kg/day as a single dose. The patient's blood count must be monitored every two weeks. (2.1)
- The dose may be increased by 5 mg/kg/day every 12 weeks until a maximum tolerated dose or 35 mg/kg/day is reached if blood counts are in an acceptable range. (2.1)
- The dose is not increased if blood counts are between the acceptable range and toxic. Discontinue DROXIA until hematologic recovery if blood counts are considered toxic. Treatment may then be resumed after reducing the dose by 2.5 mg/kg/day from the dose associated with hematological toxicity. (2.1)
- Renal impairment: Reduce the dose of DROXIA by 50% in patients with creatinine clearance less than 60 mL/min. (2.2, 8.6, 12.3)

DOSAGE FORMS AND STRENGTHS

- Capsules: 200 mg, 300 mg, and 400 mg (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- 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: Institute treatment and discontinue DROXIA if this occurs. (5.4)
- Live Vaccinations: Avoid live vaccine use in a patient taking DROXIA. (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 DROXIA, and implement treatment. (5.6)

ADVERSE REACTIONS

Most common adverse reactions (≥30%) are hematological, gastrointestinal symptoms, and anorexia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Antiretroviral drugs. (7.1)

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: MYELOSUPPRESSION AND MALIGNANCIES

1 INDICATIONS AND USAGE

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FULL PRESCRIBING INFORMATION

WARNING: MYELOSUPPRESSION AND MALIGNANCIES

Myelosuppression: DROXIA may cause severe myelosuppression. Monitor blood counts at baseline and throughout treatment. Interrupt treatment and reduce dose as necessary [see *Warnings and Precautions (5.1)*].

Malignancies: Hydroxyurea is carcinogenic. Advise sun protection and monitor patients for malignancies [see *Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

DROXIA is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in patients with sickle cell anemia with recurrent moderate to severe painful crises.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

Table 1: Dosing Recommendation Based on Blood Count

| Dosing Regimen | Dose | Dose Modification Criteria | Monitoring Parameters |
|-------------------------------------|---|--|---|
| Initial Recommended Dosing | 15 mg/kg/day as a single dose | Base dosage on the patient's actual or ideal weight, whichever is less. Monitor the patient's blood count every 2 weeks [see <i>Warnings and Precautions (5.1)</i>]. | |
| Dosing Based on Blood Counts | | | |
| In an acceptable range | Increase dose 5 mg/kg/day every 12 weeks Maximal dose: 35 mg/kg/day* *Maximal dose is the highest dose that does not produce toxic blood counts over 24 consecutive weeks. | Increase dosing only if blood counts are in an acceptable range. Do not increase if myelosuppression occurs. | Blood Counts Acceptable Range neutrophils ≥ 2500 cells/mm ³ platelets $\geq 95,000$ /mm ³ hemoglobin > 5.3 g/dL reticulocytes $\geq 95,000$ /mm ³ if the hemoglobin concentration < 9 g/dL |

Table 1: Dosing Recommendation Based on Blood Count

| Dosing Regimen | Dose | Dose Modification Criteria | Monitoring Parameters |
|--|-------------------------------|---|--|
| Between acceptable and toxic range | Do not increase dose. | If blood counts are considered toxic , discontinue DROXIA until hematologic recovery. | Blood Counts Toxic Range neutrophils <2000 cells/mm ³ platelets <80,000/mm ³ hemoglobin <4.5 g/dL reticulocytes <80,000/mm ³ if the hemoglobin concentration <9 g/dL |
| Dosing After Hematologic Recovery | Reduce dose by 2.5 mg/kg/day. | Reduce the dose from the dose associated with hematologic toxicity. May titrate up or down every 12 weeks in 2.5 mg/kg/day increments. The patient should be at a stable dose with no hematologic toxicity for 24 weeks. Discontinue the treatment permanently if a patient develops hematologic toxicity twice. | |

Patients must be able to follow directions regarding drug administration and their monitoring and care.

Fetal hemoglobin (HbF) levels may be used to evaluate the efficacy of DROXIA in clinical use. Obtain HbF levels every three to four months. Monitor for an increase in HbF of at least two-fold over the baseline value.

DROXIA causes macrocytosis, which may mask the incidental development of folic acid deficiency. Prophylactic administration of folic acid is recommended.

DROXIA is a cytotoxic drug. Follow applicable special handling and disposal procedures [*see References (15)*].

2.2 Dose Modifications for Renal Impairment

Reduce the dose of DROXIA by 50% in patients with 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)*]. Creatinine clearance values were obtained using 24-hour urine collections.

| Creatinine Clearance (mL/min) | Recommended DROXIA Initial Dose (mg/kg daily) |
|--|--|
| ≥60 | 15 |
| <60 or ESRD* | 7.5 |

* On dialysis days, administer DROXIA to patients with ESRD following hemodialysis.

Monitor the hematologic parameters closely in these patients.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 200 mg opaque blue-green capsules, imprinted with black ink “DROXIA” and “6335.”
- 300 mg opaque purple capsules, imprinted with black ink “DROXIA” and “6336.”
- 400 mg opaque reddish-orange capsules, imprinted with black ink “DROXIA” and “6337.”

4 CONTRAINDICATIONS

DROXIA is contraindicated in patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Hydroxyurea causes severe myelosuppression. Treatment with hydroxyurea should not be initiated 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.

Some patients, treated at the recommended initial dose of 15 mg/kg/day, have experienced severe or life-threatening myelosuppression.

Evaluate hematologic status prior to and during treatment with DROXIA. Provide supportive care and modify dose or discontinue DROXIA as needed. Recovery from myelosuppression is usually rapid when therapy 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, DROXIA can cause fetal harm when administered to a pregnant woman. Hydroxyurea was embryotoxic and teratogenic in rats and rabbits at doses 0.8 times and 0.3 times, respectively, the maximum recommended human daily dose on a mg/m² basis. Advise pregnant women of the potential risk to a fetus [see *Use in Specific Populations (8.1)*].²

Advise females of reproductive potential to use effective contraception during and after treatment with DROXIA for at least 6 months after therapy. Advise males of reproductive potential to use effective contraception during and after treatment with DROXIA for at least 1 year after therapy [see *Use in Specific Populations (8.1, 8.3)*].^{3,4}

5.4 Vasculitic Toxicities

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. If cutaneous vasculitic ulcers occur, institute treatment and discontinue DROXIA.

5.5 Live Vaccinations

Avoid use of live vaccine in patients taking DROXIA. Concomitant use of DROXIA 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 DROXIA. Vaccination with live vaccines in a patient receiving DROXIA may result in severe infection. Patient's antibody response to vaccines may be decreased. Consider consultation with a specialist.

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 Macrocytosis

DROXIA 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 folic acid 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 Boxed Warning and 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)*]
- Macrocytosis [*see Warnings and Precautions (5.7)*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trial Experience

In 299 patients treated for sickle cell anemia in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia, the most common adverse reactions were hematologic, with neutropenia, and low reticulocyte and platelet levels necessitating temporary cessation in almost all patients. Hematologic recovery usually occurred in two weeks.

Other adverse reactions include hair loss, macrocytosis, bleeding, and melanonychia.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of hydroxyurea in the treatment of neoplastic diseases. 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:* azoospermia, and oligospermia **Error! Bookmark not defined.**
- *Gastrointestinal disorders:* stomatitis, nausea, vomiting, diarrhea, and constipation
- *Metabolism and Nutrition disorders:* anorexia⁵
- *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 levels
- *Nervous system disorders:* headache, dizziness, drowsiness, disorientation, hallucinations, and convulsions
- *General disorders:* fever, chills, malaise, edema, and asthenia
- *Hepatobiliary disorders:* elevation of hepatic enzymes, cholestasis, and hepatitis⁶
- *Respiratory disorders:* diffuse pulmonary infiltrates, dyspnea, and pulmonary fibrosis

7 DRUG INTERACTIONS

7.1 Increased Toxicity with Concomitant Use of Antiretroviral Drugs

Pancreatitis

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, and in particular, in combination with didanosine and/or 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 antiretroviral drugs, 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 enzymes (urease, uricase, and lactate dehydrogenase) used in the determination of urea, uric acid, and lactic acid, rendering falsely elevated results of these in patients treated with hydroxyurea.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy⁷

Risk Summary

DROXIA can cause fetal harm based on findings from animal studies and the drug's mechanism of action [see *Clinical Pharmacology (12.1)*]. There are no data with DROXIA use in pregnant women to inform a drug-associated risk. In animal reproduction studies, administration of hydroxyurea to pregnant rats and rabbits during organogenesis produced embryotoxic and teratogenic effects at doses 0.8 times and 0.3 times, respectively, the maximum recommended human daily dose on a mg/m² basis (see *Data*). Advise women of the potential risk to a fetus and to avoid becoming pregnant while being treated with DROXIA.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Data

Animal Data

Hydroxyurea has been demonstrated to be a potent teratogen in a wide variety of animal models, including mice, hamsters, cats, miniature swine, dogs, and monkeys at doses within 1-fold of the human dose given on a mg/m^2 basis. Hydroxyurea is embryotoxic and causes fetal malformations (partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae) at 180 $\text{mg}/\text{kg}/\text{day}$ (about 0.8 times the maximum recommended human daily dose on a mg/m^2 basis) in rats and at 30 $\text{mg}/\text{kg}/\text{day}$ (about 0.3 times the maximum recommended human daily dose on a mg/m^2 basis) in rabbits. Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. Hydroxyurea crosses the placenta. Single doses of ≥ 375 mg/kg (about 1.7 times the maximum recommended human daily dose on a mg/m^2 basis) to rats caused growth retardation and impaired learning ability.

8.2 Lactation

Risk Summary

Hydroxyurea is excreted in human milk. Because of the potential for serious adverse reactions in a breastfed infant from hydroxyurea, including carcinogenicity, discontinue breastfeeding during treatment with DROXIA.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating DROXIA therapy.

Contraception

Females

DROXIA can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during and after treatment with DROXIA for at least 6 months after therapy. Advise females to immediately report pregnancy.

Males

DROXIA may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during and after treatment with DROXIA for at least 1 year after therapy [*see Nonclinical Toxicology (13.1)*].

Infertility

Males

Based on findings in animals and humans, male fertility may be compromised by treatment with DROXIA. Azoospermia or oligospermia, sometimes reversible, has been observed in men. Inform male patients about the possibility of sperm conservation before the start of therapy [*see Adverse Reactions (6) and Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of DROXIA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen. Hydroxyurea is excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [*see Dosage and Administration (2.2)*].

8.6 Renal Impairment

The exposure to hydroxyurea is higher in patients with creatinine clearance of less than 60 mL/min. Reduce dosage and closely monitor the hematologic parameters when DROXIA is to be administered to these patients [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

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.

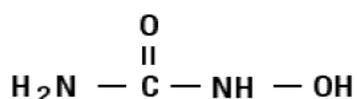
10 OVERDOSAGE

Acute mucocutaneous toxicity has been reported in patients receiving hydroxyurea at dosages 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 been observed.

11 DESCRIPTION

DROXIA[®] (hydroxyurea capsules, USP) is available for oral use as capsules containing 200 mg, 300 mg, and 400 mg hydroxyurea. Inactive ingredients include citric acid, gelatin, lactose, magnesium stearate, sodium phosphate, titanium dioxide, and capsule colorants: FD&C Blue No. 1 and FD&C Green No. 3 (200 mg capsules); D&C Red No. 28, D&C Red No. 33, and FD&C Blue No. 1 (300 mg capsules); D&C Red No. 28, D&C Red No. 33, and D&C Yellow No. 10 (400 mg capsules).

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 $\text{CH}_4\text{N}_2\text{O}_2$ and it has a molecular weight of 76.05. Its structural formula is⁸:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which hydroxyurea produces its cytotoxic and cytoreductive effects is not known. However, various studies support 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.

The mechanisms by which DROXIA produces its beneficial effects in patients with sickle cell anemia (SCA) are uncertain. Known pharmacologic effects of DROXIA that may contribute to its beneficial effects include increasing hemoglobin F levels in red blood cells (RBCs), decreasing neutrophils, increasing the water content of RBCs, increasing deformability of sickled cells, and altering the adhesion of RBCs to endothelium.

12.3 Pharmacokinetics

Absorption

Following oral administration of DROXIA, hydroxyurea reaches peak plasma concentrations in 1 to 4 hours. Mean peak plasma concentrations and AUCs increase more than proportionally with increase of dose.

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 leukocytes 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.

Specific Populations

Renal Impairment

The effect of renal impairment on the pharmacokinetics of hydroxyurea was assessed in adult patients with sickle cell disease and renal impairment. Patients with normal renal function (creatinine clearance [CrCl] >80 mL/min), mild (CrCl 50-80 mL/min), moderate (CrCl =30-50 mL/min), or severe (<30 mL/min) renal impairment received a single oral dose of 15 mg/kg hydroxyurea. Creatinine clearance values were obtained using 24-hour urine collections. Patients with 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. The exposure to hydroxyurea (mean AUC) in patients with CrCl <60 mL/min and those with ESRD was 64% higher than in patients with normal renal function (CrCl >60 mL/min). Reduce the dose of DROXIA when it is administered to patients with creatinine clearance of <60 mL/min or with ESRD following hemodialysis [see *Dosage and Administration (2.2) and Use in Specific Populations (8.6)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Conventional long-term studies to evaluate the carcinogenic potential of DROXIA have not been performed. However, intraperitoneal administration of 125 to 250 mg/kg hydroxyurea (about 0.6-1.2 times the maximum recommended human oral daily dose on a mg/m² basis) thrice weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to control. Hydroxyurea is mutagenic *in vitro* to bacteria, fungi, protozoa, and mammalian cells. Hydroxyurea is clastogenic *in vitro* (hamster cells, human lymphoblasts) and *in vivo* (SCE assay in rodents, mouse micronucleus assay). Hydroxyurea causes the transformation of rodent embryo cells to a tumorigenic phenotype.

Hydroxyurea administered to male rats at 60 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m² basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

14 CLINICAL STUDIES

The efficacy of hydroxyurea in sickle cell anemia was assessed in a large clinical study (Multicenter Study of Hydroxyurea in Sickle Cell Anemia) (see Table 2).

The study was a randomized, double-blind, placebo-controlled trial that evaluated 299 adult patients (≥ 18 years) with moderate to severe disease (≥ 3 painful crises yearly). The trial was stopped by the Data Safety Monitoring Committee, after accrual was completed but before the scheduled 24 months of follow-up was completed in all patients, based on observations of fewer painful crises among patients receiving hydroxyurea.

Compared to placebo treatment, treatment with hydroxyurea resulted in a significant decrease in the yearly rate of painful crises, the yearly rate of painful crises requiring hospitalization, the incidence of chest syndrome, the number of patients transfused, and units of blood transfused. Hydroxyurea treatment significantly increased the median time to both first and second painful crises.

Although patients with 3 or more painful crises during the preceding 12 months were eligible for the study, most of the benefit in crisis reduction was seen in the patients with 6 or more painful crises during the preceding 12 months.

Table 2: Results from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia

| Event | Hydroxyurea (N=152) | Placebo (N=147) | Percent Change Versus Placebo | P-value |
|--|------------------------|--------------------|----------------------------------|---------|
| Median yearly rate of painful crises* | 2.5 | 4.6 | -46 | =0.001 |
| Median yearly rate of painful crises requiring hospitalization | 1.0 | 2.5 | -60 | =0.0027 |
| Median time to first painful crisis (months) | 2.76 | 1.35 | +104 | =0.014 |
| Median time to second painful crisis (months) | 6.58 | 4.13 | +59 | =0.0024 |
| Incidence of chest syndrome (# episodes) | 56 | 101 | -45 | =0.003 |
| Number of patients transfused | 55 | 79 | -30 | =0.002 |
| Number of units of blood transfused | 423 | 670 | -37 | =0.003 |

* A painful crisis was defined in the study as acute sickling-related pain that resulted in a visit to a medical facility, that lasted more than 4 hours, and that required treatment with a parenteral narcotic or NSAID. Chest syndrome, priapism, and hepatic sequestration were also included in this definition.

In patients with SCA treated with hydroxyurea, fetal hemoglobin (HbF) increases 4 to 12 weeks after initiation of treatment. In general, average HbF levels correlate with dose and plasma level with possible plateauing at higher dosages.

A clear relation between reduction in crisis frequency and increased HbF or F-cell levels has not been demonstrated. The dose-related cytoreductive effects of hydroxyurea, particularly on neutrophils, was the factor most strongly correlated with reduced crisis frequency.

15 REFERENCES

OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DROXIA[®] (hydroxyurea capsules, USP) is supplied in HDPE bottles with a plastic safety screw cap. Each bottle contains 60 capsules. DROXIA is supplied in the following strengths:

200 mg opaque blue-green capsules, marked in black ink with “**DROXIA**” and “**6335**” (NDC 0003-6335-17).

300 mg opaque purple capsules, marked in black ink with “**DROXIA**” and “**6336**” (NDC 0003-6336-17).

400 mg opaque reddish-orange capsules, marked in black ink with “**DROXIA**” and “**6337**” (NDC 0003-6337-17).

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature]. Keep tightly closed.

16.3 Handling and Disposal

DROXIA is a cytotoxic drug. Follow applicable special handling and disposal procedures [*see References (15)*].

To decrease the risk of contact, advise caregivers to wear disposable gloves when handling DROXIA or bottles containing DROXIA. Wash hands with soap and water before and after contact with the bottle or capsules when handling DROXIA. Do not open DROXIA capsules. Avoid exposure to crushed or opened capsules. If contact with crushed or opened capsules occurs on the skin, wash affected area immediately and thoroughly with soap and water. If contact with crushed or opened capsules occurs on the eye(s), the affected area should be flushed thoroughly with water or isotonic eyewash designated for that purpose for at least 15 minutes. If the powder from the capsule is spilled, immediately wipe it up with a damp disposable towel and discard in a closed container, such as a plastic bag; as should the empty capsules. The spill areas should then be cleaned three times using a detergent solution followed by clean water. Keep the medication away from children and pets. Contact your doctor for instructions on how to dispose of outdated capsules.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- There is a risk of myelosuppression. Monitoring blood counts every two weeks throughout the duration of therapy should be emphasized to patients taking DROXIA [see *Warnings and Precautions (5.1)*]. Advise patients to report signs and symptoms of infection or bleeding immediately.
- Advise patients that there is a risk of cutaneous vasculitic toxicities and secondary malignancies including leukemia and skin cancers. Advise use of sun protection [see *Warnings and Precautions (5.2, 5.4)*].
- Advise patients to inform their healthcare provider if they have received or are planning to receive vaccinations while taking DROXIA as this may result in a severe infection [see *Warnings and Precautions (5.5)*].⁹
- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy. Advise females and males of reproductive potential to use contraception during and after treatment with DROXIA [see *Warnings and Precautions (5.3)* and *Use in Specific Populations (8.1, 8.3)*].
- Advise females to discontinue breastfeeding during treatment with DROXIA [see *Use in Specific Populations (8.3)*].
- Patients with HIV infection should contact their physician for signs and symptoms of pancreatitis, hepatic events, and peripheral neuropathy [see *Warnings and Precautions (5.6)*].

Manufactured for:

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

Product of Italy

[print code]

Patient Information
DROXIA[®] (drock-SEE-yuh)
(hydroxyurea capsules, USP)

Read this Patient Information before you start using DROXIA (hydroxyurea) and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. You and your healthcare provider should talk about DROXIA when you start taking it and at regular checkups.

What is the most important information I should know about DROXIA?

DROXIA can cause serious side effects including:

- Low blood counts are common with DROXIA, including low red blood cells, white blood cells, and platelets, and can be severe and life-threatening. If your white blood cell count becomes very low, you are at increased risk for infection. Your healthcare provider will check your blood cell counts before and during treatment with DROXIA. Your healthcare provider may change your dose or tell you to stop taking DROXIA if you have low blood cell counts. Tell your healthcare provider right away if you get any of the following symptoms:
 - fever
 - chills
 - body aches
 - feeling very tired
 - shortness of breath
 - bleeding
- **Cancer.** Some people have developed cancer, such as leukemia and skin cancer, after taking DROXIA for a long time. Your healthcare provider will check you for cancer. You should protect your skin from the sun using sunblock, hats, and sun-protective clothing.

DROXIA may cause harm to your unborn baby.

For females taking DROXIA who can become pregnant:

- You should talk with your healthcare provider about the risks of DROXIA to your unborn child.
- You should use effective birth control during and after treatment with DROXIA for at least 6 months after treatment.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant.

For males taking DROXIA:

- Males should use effective contraception during and after treatment with DROXIA for at least 1 year after therapy.

For females NOT taking DROXIA who can become pregnant:

- You should ensure that your male partner, who is/has taken DROXIA, uses effective contraception during and after treatment for at least 1 year after therapy.

DROXIA may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.

See “**What are the possible side effects of DROXIA?**” for more information about side effects.

What is DROXIA?

DROXIA is a prescription medicine that is used to reduce the frequency of painful crises and reduce the need for blood transfusions in people with sickle cell anemia with recurrent moderate to severe painful crises.

It is not known if DROXIA is safe and effective in children.

Who should not take DROXIA?

Do not take DROXIA if you are allergic to hydroxyurea or any of the ingredients in DROXIA. See the end of this leaflet for a list of the ingredients in DROXIA.

Before taking DROXIA, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems or are receiving hemodialysis
- have liver problems
- have human immunodeficiency virus (HIV). Taking DROXIA with certain HIV medicines can cause serious reactions and may lead to death.
- have increased level of uric acid in your blood (hyperuricemia)
- have a history of receiving interferon therapy or are currently receiving interferon therapy
- are pregnant or plan to become pregnant. See “**What is the most important information I should know about DROXIA?**”
- are breastfeeding or plan to breastfeed. DROXIA can pass into your breast milk. Do not breastfeed during treatment with DROXIA. Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take an antiretroviral medicine.

Taking DROXIA with certain antiretroviral medicines can cause serious side effects and may lead to death. Tell your healthcare provider if you received or are planning to receive a vaccination.

How should I take DROXIA?

- Take DROXIA exactly as your healthcare provider tells you.
- DROXIA is taken 1 time a day.
- Your healthcare provider will determine the right starting dose of DROXIA for you based on your weight. Your dose will then be increased slowly to your maximum tolerated dose (a dose that does not produce severely low blood counts).
- If you take too much DROXIA, call your healthcare provider or go to the nearest hospital emergency room right away.
- DROXIA is a medicine that must be handled with care. People who are not taking DROXIA should not be exposed to it. To decrease the risk of exposure, you or your caregivers should do the following when handling DROXIA:
 - Wear disposable gloves when handling DROXIA capsules or bottles containing DROXIA.
 - Wash your hands before and after handling DROXIA capsules or bottles containing DROXIA.
 - Do not open the capsules.
 - Avoid contact with crushed or opened capsules. If contact from crushed or opened capsules happens on the skin, wash the skin area right away with soap and water. If contact from crushed or opened capsules happens on the eye(s), flush the eye(s) thoroughly with water or isotonic eyewash designated for that purpose for at least 15 minutes.
 - If the powder from the capsule is spilled, wipe it up right away with a damp disposable towel, and throw it away in a closed container, such as a plastic bag; as should the empty capsules. The spill areas should then be cleaned three times using a detergent solution followed by clean water.

What are the possible side effects of DROXIA?

DROXIA may cause serious side effects, including:

- See **“What is the most important information I should know about DROXIA?”**
- Skin ulcers have happened in people who take DROXIA. This has occurred most often in people who receive interferon therapy or have a history of interferon therapy. Your healthcare provider will stop treatment with DROXIA if you develop any skin ulcers.

The most common side effects of DROXIA include:

- hair loss

- enlarged red blood cells (macrocytosis). Macrocytosis can make it difficult to detect a decrease of folic acid in people taking DROXIA. Your healthcare provider may prescribe a folic acid supplement for you.
- bleeding
- brown or black colored nails

These are not all the possible side effects of DROXIA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How Should I store DROXIA?

- Store DROXIA at room temperature between 68°F to 77°F (20°C to 25°C). Keep the bottle tightly closed.
- Call your healthcare provider for instructions on how to throw away (dispose of) DROXIA that is out of date or no longer needed.

Keep DROXIA and all medicines out of the reach of children. Keep DROXIA away from pets.

General information about the safe and effective use of DROXIA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use DROXIA for a condition for which it was not prescribed. Do not give DROXIA to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about DROXIA that is written for health professionals.

What are the ingredients of DROXIA?

Active ingredient: hydroxyurea

Inactive ingredients: citric acid, gelatin, lactose, magnesium stearate, sodium phosphate, titanium dioxide, and capsule colorants: FD&C Blue No. 1 and FD&C Green No. 3 (200 mg capsules); D&C Red No. 28, D&C Red No. 33, and FD&C Blue No. 1 (300 mg capsules); D&C Red No. 28, D&C Red No. 33, and D&C Yellow No. 10 (400 mg capsules).

Manufactured for: Bristol-Myers Squibb Company, Princeton, New Jersey 08543 USA
Product of Italy

For more information, go to www.BMS.com or call 1-800-721-5072.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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