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: **DROXIA is carcinogenic. Advise sun protection and monitor patients for malignancies. (5.3)**

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

Warnings and Precautions, Hemolytic Anemia (5.2)	07/2021
Warnings and Precautions, Malignancies (5.3)	02/2021

----------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 once daily. Monitor the patient's blood count 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----------

- Hemolytic anemia: Monitor blood counts throughout treatment. If hemolysis persists, discontinue DROXIA. (5.2)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)
- Vasculitic toxicities: Institute treatment and discontinue DROXIA if this occurs. (5.5)
- Live Vaccinations: Avoid live vaccine use in a patient taking DROXIA. (5.6)
- 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. (5.7)

----------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)
- Laboratory Test Interference. (7.2)

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

- Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved medication guide

Revised: 07/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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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: **DROXIA is carcinogenic. Advise sun protection and monitor patients for malignancies *[see Warnings and Precautions (5.3)]*.**

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 once daily based on the patient's actual or ideal weight, whichever is less.		Monitor the patient's blood count every 2 weeks *[see Warnings and Precautions (5.1)]*.
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 ≥95,000/mm^3 hemoglobin >5.3 g/dL reticulocytes ≥95,000/mm^3 if the hemoglobin concentration <9 g/dL

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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.	

Swallow DROXIA capsules whole. Do NOT open, break, or chew capsules because DROXIA is a cytotoxic drug. 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.

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Creatinine Clearance (mL/min)	Recommended DROXIA Initial Dose (mg/kg once 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 DROXIA 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 Hemolytic Anemia

Cases of hemolytic anemia in patients treated with hydroxyurea for myeloproliferative diseases have been reported *[see Adverse Reactions (6.1)]*. Patients who develop acute jaundice or hematuria in the presence of persistent or worsening of anemia should have laboratory tests evaluated for hemolysis (e.g., measurement of serum lactate dehydrogenase, haptoglobin, reticulocyte, unconjugated bilirubin levels, urinalysis, and direct and indirect antiglobulin [Coombs] tests). In the setting of confirmed diagnosis of hemolytic anemia and in the absence of other causes, discontinue DROXIA.

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5.3 Malignancies

Hydroxyurea is a human carcinogen. In patients receiving long-term hydroxyurea for myeloproliferative disorders, secondary leukemia has been reported.

Secondary leukemia has also been reported in patients treated with long-term hydroxyurea for sickle cell disease. Leukemia has also been reported in patients with sickle cell disease and no prior history of treatment with hydroxyurea.

All patients using DROXIA should be followed up on a long-term basis with regular blood counts to detect development of leukemia.

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.

5.4 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/m^2 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 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)]*.

5.5 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.

5.6 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.

5.7 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)]*.

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5.8 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 B_{12} or folic acid deficiency. This may mask the diagnosis of pernicious anemia. Prophylactic administration of folic acid is recommended.

5.9 Pulmonary Toxicity

Interstitial lung disease including pulmonary fibrosis, lung infiltration, pneumonitis, and alveolitis/allergic alveolitis (including fatal cases) have been reported in patients treated for myeloproliferative neoplasm. Safety and effectiveness have not been established for the use of DROXIA in the treatment of myeloproliferative neoplasms and the use is not approved by the FDA. Monitor patients developing pyrexia, cough, dyspnea, or other respiratory symptoms frequently, investigate and treat promptly. Discontinue DROXIA and manage with corticosteroids. *[see Adverse Reactions (6.1)]*.

5.10 Laboratory Test Interference

Interference with Uric Acid, Urea, or Lactic Acid Assays is possible, rendering falsely elevated results of these in patients treated with hydroxyurea *[see Drug Interactions* (7.2)*]*.

6 ADVERSE REACTIONS

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

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Hemolytic anemia *[see Warnings and Precautions (5.2)]*
- Malignancies *[see Warnings and Precautions (5.3)]*
- Vasculitic toxicities *[see Warnings and Precautions (5.5)]*
- Risks with concomitant use of antiretroviral drugs *[see Warnings and Precautions (5.7)]*
- Macrocytosis *[see Warnings and Precautions (5.8)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.9)]*

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.

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6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval 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
- *Gastrointestinal disorders:* stomatitis, nausea, vomiting, diarrhea, and constipation
- *Metabolism and Nutrition disorders:* anorexia
- *Skin and subcutaneous tissue disorders:* maculopapular rash, skin ulceration, cutaneous lupus erythematosus, dermatomyositis-like skin changes, peripheral and facial erythema, hyperpigmentation, nail 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 hepatitis
- *Respiratory disorders:* diffuse pulmonary infiltrates, dyspnea, and pulmonary fibrosis, interstitial lung disease, pneumonitis, alveolitis, allergic alveolitis and cough
- *Immune disorders:* systemic lupus erythematosus
- *Hypersensitivity:* Drug-induced fever (pyrexia) (>39°C, >102°F) requiring hospitalization has been reported concurrently with gastrointestinal, pulmonary, musculoskeletal, hepatobiliary, dermatological or cardiovascular manifestations. Onset typically occurred within 6 weeks of initiation and resolved upon discontinuation of hydroxyurea. Upon re-administration fever re-occurred typically within 24 hours.
- *Blood and lymphatic system disorders:* hemolytic anemia

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 DROXIA in patients who develop signs and symptoms of pancreatitis.

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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 Laboratory 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 Pregnancy

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/m^2 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 mg/kg/day (about 0.8 times the maximum recommended human daily dose on a mg/m^2 basis) in rats and at 30 mg/kg/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

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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.

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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.

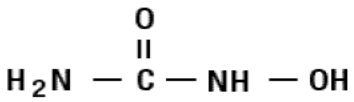
10 OVERDOSAGE

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 $CH_4N_2O_2$ and it has a molecular weight of 76.05. Its structural formula is:



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

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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)]*.

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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/m^2 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/m^2 basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

14 CLINICAL STUDIES

The efficacy of DROXIA 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

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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 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 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep tightly closed.

Reference ID: 4836120

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 (Medication Guide).

- There is a risk of myelosuppression. Monitoring blood counts every two weeks throughout the duration of therapy should be emphasized to patients taking DROXIA. Advise patients to report signs and symptoms of infection or bleeding immediately *[see Warnings and Precautions (5.1)]*.
- Advise patients of the risk of hemolytic anemia. Advise patients that they will have blood tests to evaluate for this if they develop persistent anemia. *[see Warnings and Precautions (5.2)]*.
- 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 (5.3, 5.5)]*.
- 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 (5.6)]*.
- 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 (5.4) and Use in Specific Populations (8.1, 8.3)]*.
- Advise females to discontinue breastfeeding during treatment with DROXIA *[see Use in Specific Populations (8.2)]*.
- Patients with HIV infection should contact their physician for signs and symptoms of pancreatitis, hepatic events, and peripheral neuropathy *[see Warnings and Precautions (5.7)]*.

Reference ID: 4836120

- Advise patients of the symptoms of potential pulmonary toxicity and instruct them to seek prompt medical attention in the event of pyrexia, cough, dyspnea, or other respiratory symptoms *[see Warnings and Precautions (5.9)]*.

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

Reference ID: 4836120

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----------

Warnings and Precautions, Hemolytic Anemia (5.2) 07/2021

----------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 blood counts at baseline and throughout treatment. Interrupt treatment and reduce dose as necessary. (5.1)
- Hemolytic anemia: Monitor blood counts throughout treatment. If hemolysis persists, discontinue HYDREA. (5.2)
- Malignancies: Advise protection from sun exposure and monitor for secondary malignancies. (5.3)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)
- Vasculitic toxicities: Discontinue HYDREA and initiate treatment if this occurs. (5.5)
- Live Vaccinations: Avoid live vaccine use in a patient taking HYDREA. (5.6)
- 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. (5.7)
- Radiation recall: Monitor for skin erythema in patients who previously received radiation and manage symptomatically. (5.8)

----------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)
- Laboratory Test Interference. (7.2)

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

- Lactation: Advise women not to breastfeed. (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: 07/2021

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15 REFERENCES
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*Sections or subsections omitted from the full prescr bing information are not listed.

Reference ID: 4836120

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)]*.

Swallow HYDREA capsules whole. Do NOT open, break, or chew capsules because HYDREA is a cytotoxic drug.

Prophylactic administration of folic acid is recommended *[see Warnings and Precautions (5.8)]*.

Monitor blood counts at least once a week during HYDREA therapy. Severe anemia must be corrected before initiating therapy with HYDREA.

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 (5.5)]*

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 once 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 HYDREA 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 HYDREA 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 Hemolytic Anemia

Cases of hemolytic anemia in patients treated with HYDREA for myeloproliferative diseases have been reported *[see Adverse Reactions (6.1)]*. Patients who develop acute jaundice or hematuria in the presence of persistent or worsening of anemia should have laboratory tests evaluated for hemolysis (e.g., measurement of serum lactate dehydrogenase, haptoglobin, reticulocyte, unconjugated bilirubin levels, urinalysis, and direct and indirect antiglobulin [Coombs] tests). In the setting of confirmed diagnosis of hemolytic anemia and in the absence of other causes, discontinue HYDREA.

5.3 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.

5.4 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, HYDREA 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/m^2 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 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)]*.

5.5 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.

5.6 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.

5.7 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)]*.

5.8 Radiation Recall

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

5.9 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 B_{12} or folic acid deficiency. This may mask the diagnosis of pernicious anemia. Prophylactic administration of folic acid is recommended.

5.10 Pulmonary Toxicity

Interstitial lung disease including pulmonary fibrosis, lung infiltration, pneumonitis, and alveolitis/allergic alveolitis (including fatal cases) have been reported in patients treated for myeloproliferative neoplasm. Monitor patients developing pyrexia, cough, dyspnea, or other respiratory symptoms frequently, investigate and treat promptly. Discontinue HYDREA and manage with corticosteroids *[see Adverse Reactions (6.1)]*.

5.11 Laboratory Test Interference

Interference with Uric Acid, Urea, or Lactic Acid Assays is possible, rendering falsely elevated results of these in patients treated with hydroxyurea *[see Drug Interactions (7.2)]*.

6 ADVERSE REACTIONS

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

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Hemolytic anemia *[see Warnings and Precautions (5.2)]*
- Malignancies *[see Warnings and Precautions (5.3)]*
- Vasculitic toxicities *[see Warnings and Precautions (5.5)]*
- Risks with concomitant use of antiretroviral drugs *[see Warnings and Precautions (5.7)]*
- Radiation recall *[see Warnings and Precautions (5.8)]*
- Macrocytosis *[see Warnings and Precautions (5.9)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.10)]*

6.1 Postmarketing Experience

The following adverse reactions have been identified during post-approval 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
- *Gastrointestinal disorders:* stomatitis, nausea, vomiting, diarrhea, and constipation
- *Metabolism and Nutrition disorders:* anorexia, tumor lysis syndrome
- *Skin and subcutaneous tissue disorders:* maculopapular rash, skin ulceration, cutaneous lupus erythematosus, dermatomyositis-like skin changes, peripheral and facial erythema, hyperpigmentation, nail 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 hepatitis
- *Respiratory disorders:* diffuse pulmonary infiltrates, dyspnea, and pulmonary fibrosis, interstitial lung disease, pneumonitis, alveolitis, allergic alveolitis and cough
- *Immune disorders:* systemic lupus erythematosus
- *Hypersensitivity:* Drug-induced fever (pyrexia) (>39°C, >102°F) requiring hospitalization has been reported concurrently with gastrointestinal, pulmonary, musculoskeletal, hepatobiliary, dermatological or cardiovascular manifestations. Onset typically occurred within 6 weeks of

initiation and resolved upon discontinuation of hydroxyurea. Upon re-administration fever re-occurred typically within 24 hours.

- *Blood and lymphatic system disorders:* hemolytic anemia

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/mm^3) 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 HYDREA 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 Laboratory 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 Pregnancy

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 mg/kg/day (about 0.8 times the maximum recommended human daily dose on a mg/m^2 basis) in rats and at 30 mg/kg/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 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

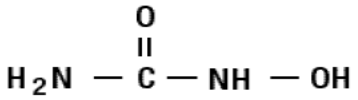
Acute mucocutaneous toxicity has been reported in patients receiving hydroxyurea at dosages several times the therapeutic dose. Soreness, violet erythema, edema on palms and soles followed

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 $CH_4N_2O_2$ and it has a molecular weight of 76.05. Its structural formula is:



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/m^2 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/m^2 basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

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 20°C-25°C (68°F-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. Advise patients to report signs and symptoms of infection or bleeding immediately *[see Warnings and Precautions (5.1)]*.
- Advise patients of the risk of hemolytic anemia. Advise patients that they will have blood tests to evaluate for this if they develop persistent anemia *[see Warnings and Precautions (5.2)]*.
- Advise patients that there is a risk of cutaneous vasculitic toxicities and secondary malignancies including leukemia and skin cancers *[see Warnings and Precautions (5.3, 5.5)]*.
- 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 (5.4) 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 (5.6)]*.
- Advise females to discontinue breastfeeding during treatment with HYDREA *[see Use in Specific Populations (8.2)]*.
- Patients with HIV infection should contact their physician for signs and symptoms of pancreatitis, hepatic events, and peripheral neuropathy *[see Warnings and Precautions (5.7)]*.
- Post-irradiation erythema can occur in patients who have received previous irradiation therapy *[see Warnings and Precautions (5.8)]*.
- Advise patients of the symptoms of potential pulmonary toxicity and instruct them to seek prompt medical attention in the event of pyrexia, cough, dyspnea, or other respiratory symptoms *[see Warnings and Precautions (5.10)]*.

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

2 OF 5 N° 015519

GTIN: 00300036335177
S/N:
LOT:
EXP.:

DM
10X10 mm

3001476A3

60 CAPSULES NDC 0003-6335-17

DROXIA®
(hydroxyurea capsules, USP)

200 mg per capsule

Rx only
CAUTION: Cytotoxic Agent

Bristol Myers Squibb

Wear disposable gloves when handling DROXIA or bottles containing DROXIA.

Do NOT open, break, or chew capsules.

Each capsule contains 200 mg hydroxyurea.

Dosage: See package insert for full prescribing information.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

Keep tightly closed. Dispense in tight containers.

Do not use if inner seal of bottle is broken or missing.

60 CAPSULES NDC 0003-6335-17

DROXIA®
(hydroxyurea capsules, USP)

200 mg per capsule

Rx only
CAUTION: Cytotoxic Agent

Bristol Myers Squibb

AB14

N
3 00036 33517 7

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

Product of Italy

1375898A4

2 OF 5 N° 015519

Reference ID: 4836120

Information for Serialization

2/5 CODE № 3467

Wear disposable gloves when handling DROXIA or bottles containing DROXIA. Do NOT open, break, or chew capsules.
Each capsule contains 200 mg hydroxyurea.
Dosage: See package insert for full prescribing information.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].
Keep tightly closed. Dispense in tight containers.
Do not use if inner seal of bottle is broken or missing.

60 CAPSULES **NDC 0003-6335-17**

DROXIA®
(hydroxyurea capsules, USP)

200 mg per capsule

Rx only

CAUTION: Cytotoxic Agent

Bristol Myers Squibb

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

N(01)0 03 0003 6335 17 7

1050992A7

Lot:

Exp.:

Reference ID: 4836120

2 OF 5 N° 015518

GTIN: 00300036336174
S/N:
LOT:
EXP.:

DM
10X10 mm

3001475A3

AB14

60 CAPSULES NDC 0003-6336-17

DROXIA®
(hydroxyurea capsules, USP)

300 mg per capsule

Rx only
CAUTION: Cytotoxic Agent

Bristol Myers Squibb

Wear disposable gloves when handling DROXIA or bottles containing DROXIA.

Do NOT open, break, or chew capsules.

Each capsule contains 300 mg hydroxyurea.

Dosage: See package insert for full prescribing information.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

Keep tightly closed. Dispense in tight containers.

Do not use if inner seal of bottle is broken or missing.

60 CAPSULES NDC 0003-6336-17

DROXIA®
(hydroxyurea capsules, USP)

300 mg per capsule

Rx only
CAUTION: Cytotoxic Agent

Bristol Myers Squibb

N
3 00036 33617 4

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

Product of Italy

1375845A4

2 OF 5 N° 015518

Reference ID: 4836120

Information for Serialization

2 of 5 CODE № 3468

Wear disposable gloves when handling DROXIA or bottles containing DROXIA. Do NOT open, break, or chew capsules.
Each capsule contains 300 mg hydroxyurea.
Dosage: See package insert for full prescribing information.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].
Keep tightly closed. Dispense in tight containers.
Do not use if inner seal of bottle is broken or missing.

60 CAPSULES NDC 0003-6336-17

DROXIA®
(hydroxyurea capsules, USP)

300 mg per capsule

Rx only

CAUTION: Cytotoxic Agent

Bristol Myers Squibb

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

H0509GA7

N(01)0 03 0003 6336 17 4

Lot:

Exp.:

Reference ID: 4836120

2 OF 5 N° 015517

QUIET ZONE
DM
10x10 mm

GTIN: 00300036337171
S/N:
LOT:
EXP.:

3001474A3

F4

60 CAPSULES NDC 0003-6337-17

DROXIA®
(hydroxyurea capsules, USP)

400 mg per capsule

Rx only
CAUTION: Cytotoxic Agent

Bristol Myers Squibb

Wear disposable gloves when handling DROXIA or bottles containing DROXIA.

Do NOT open, break, or chew capsules.

Each capsule contains 400 mg hydroxyurea.

Dosage: See package insert for full prescribing information.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

Keep tightly closed. Dispense in tight containers.

Do not use if inner seal of bottle is broken or missing.

60 CAPSULES NDC 0003-6337-17

DROXIA®
(hydroxyurea capsules, USP)

400 mg per capsule

Rx only
CAUTION: Cytotoxic Agent

Bristol Myers Squibb

N
3 00036 33717 1

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

Product of Italy

1375899A3

2 OF 5 N° 015517

Reference ID: 4836120

Attention:
- The elements in the "Text level" must be modified according

2 of 5 CODE № 3469

1050994A6

Wear disposable gloves when handling DROXIA or bottles containing DROXIA. Do NOT open, break, or chew capsules.

Each capsule contains 400 mg hydroxyurea.

Dosage: See package insert for full prescribing information.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

Keep tightly closed. Dispense in tight containers.

Do not use if inner seal of bottle is broken or missing.

60 CAPSULES **NDC 0003-6337-17**

DROXIA®

(hydroxyurea capsules, USP)

400 mg per capsule

Rx only

CAUTION: Cytotoxic Agent

Bristol Myers Squibb

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

3 0003 6337 17 1

Lot:

Exp.:

Reference ID: 4836120

CODE 2/5 N° 015520

100 CAPSULES NDC 0003-0830-50

HYDREA®
(hydroxyurea capsules, USP)

500 mg per capsule

Rx only

CAUTION: Cytotoxic Agent

Bristol Myers Squibb

Wear disposable gloves when handling HYDREA or bottles containing HYDREA.

Do NOT open, break, or chew capsules.

Bulk Container–Not For Household Dispensing

Each capsule contains 500 mg hydroxyurea.

Dosage: See package insert for full prescribing information.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

Keep tightly closed. Dispense in tight containers.

Do not use if inner seal of bottle is broken or missing.

100 CAPSULES NDC 0003-0830-50

HYDREA®
(hydroxyurea capsules, USP)

500 mg per capsule

Rx only

CAUTION: Cytotoxic Agent

Bristol Myers Squibb

N 3 0003 0830 50 0

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

Product of Italy

1375935A3

CODE 2/5 N° 015520

Attention:
- The elements in the "Text level" must be modified according to the needs of the graphics.
- The elements in the "Color Profile" must not be changed.
It can only be colored differently.

Reference ID: 4836120

Code 2/5 N° 3470

Wear disposable gloves when handling HYDREA or bottles containing HYDREA. Do NOT open, break, or chew capsules.

Bulk Container–Not For Household Dispensing

Each capsule contains 500 mg hydroxyurea.

Dosage: See package insert for full prescribing information.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

Keep tightly closed. Dispense in tight containers. Do not use if inner seal of bottle is broken or missing.

100 CAPSULES **NDC 0003-0830-50**

HYDREA®

(hydroxyurea capsules, USP)

500 mg per capsule

Rx only

CAUTION: Cytotoxic Agent

Bristol Myers Squibb

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

1050995A5

3 0003 0830 50 0

Lot:

Exp.:

Reference ID: 4836120

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/s/

ROSANNA W SETSE
08/05/2021 08:31:02 AM