

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**PURIXAN® (mercaptopurine) oral suspension**  
**Initial U.S. Approval: 1953**

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

Warnings and Precautions, Treatment  
Related Malignancies (5.5) 05/2017

Warnings and Precautions, Macrophage  
Activation Syndrome (5.6) 05/2017

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

PURIXAN (mercaptopurine) is a nucleoside metabolic inhibitor indicated for the treatment of patients with acute lymphoblastic leukemia (ALL) as a component of a combination maintenance therapy regimen. (1.1)

### ----- DOSAGE AND ADMINISTRATION -----

The starting dose of PURIXAN in multi-agent combination chemotherapy maintenance regimens is 1.5 to 2.5 mg/kg (50 to 75 mg/m<sup>2</sup>) as a single daily dose. Use absolute neutrophil count to guide dosing. (2.1)

### ---- DOSAGE FORMS AND STRENGTHS----

Oral suspension: 2000 mg/100 mL (20 mg/mL) (3)

### ----- CONTRAINDICATIONS-----

- None

### ----WARNINGS AND PRECAUTIONS ----

- Myelosuppression: Monitor complete blood count (CBC) and adjust the dose of PURIXAN for severe neutropenia and thrombocytopenia. Evaluate patients with repeated severe myelosuppression for thiopurine S–methyltransferase (TPMT) deficiency.

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## FULL PRESCRIBING INFORMATION

### 1. INDICATIONS AND USAGE

#### 1.1 Acute Lymphatic Leukemia

PURIXAN (mercaptopurine) is indicated for the treatment of patients with acute lymphoblastic leukemia as part of a combination regimen.

### 2. DOSAGE AND ADMINISTRATION

#### 2.1 Maintenance Therapy

The recommended starting dose of PURIXAN in multi-agent combination chemotherapy maintenance regimens is 1.5 to 2.5 mg/kg (50 to 75 mg/m<sup>2</sup>) as a single daily dose.

After initiating PURIXAN, continuation of appropriate dosing requires periodic monitoring of absolute neutrophil count (ANC) and platelet count to assure sufficient drug exposure (that is to maintain ANC at a desirable level) and to adjust for excessive hematological toxicity.

#### 2.2 Dosage in TPMT-deficient Patients

Patients with inherited little or no thiopurine S–methyltransferase (TPMT) activity are at increased risk for severe mercaptopurine toxicity from conventional doses of mercaptopurine and generally require dose reduction. Testing for TPMT gene polymorphism should be considered in patients who experience severe bone marrow toxicities [see *Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)*].

Homozygous deficient patients may require up to a 90% dosage reduction (10% of the standard PURIXAN dose). Most patients with heterozygous TPMT deficiency tolerated recommended mercaptopurine doses, but some require dose reduction based on toxicities.

#### 2.3 Administration Instructions

Prior to initiation of PURIXAN and on each visit to the clinic, train patients or caregivers on proper handling, storage, administration, disposal and clean-up of accidental spillage of the medication. Since PURIXAN is supplied with 1 mL and 5 mL oral dispensing syringes, provide appropriate instructions regarding which syringe to use and how to administer a specified dose.

The bottle should be shaken vigorously for at least 30 seconds to ensure the oral suspension is well mixed.

PURIXAN is a pink to brown viscous oral suspension.

Once opened, PURIXAN should be used within 8 weeks.

Patients with homozygous-TPMT deficiency require substantial dose reductions of PURIXAN. (5.1)

- Hepatotoxicity: Monitor transaminases and bilirubin. Hold or adjust the dose of PURIXAN. (5.2)

- Immunosuppression: Due to the immunosuppression associated with maintenance chemotherapy for ALL, response to all vaccines may be diminished and there is a risk of infection with live virus vaccines. Consult immunization guidelines for immunocompromised children. (5.3)
- Embryo-fetal toxicity: PURIXAN can cause fetal harm. Advise women of potential risk to a fetus. (5.4)

- Treatment Related Malignancies: Aggressive and fatal cases of hepatosplenic T-cell lymphoma have occurred. (5.5)

- Hemophagocytic Lymphohistiocytosis: Monitor for and treat promptly; discontinue PURIXAN. (5.6)

### ----- ADVERSE REACTIONS -----

The most common adverse reaction (> 20% of patients) is myelosuppression including anemia, neutropenia, lymphopenia and thrombocytopenia. Adverse reactions occurring in 5-20% of patients include anorexia, nausea, vomiting, diarrhea, malaise and rash. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Rare Disease Therapeutics, Inc. at 888-470-0578 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

### ----- DRUG INTERACTIONS -----

- Allopurinol: Avoid use. (7.1)
- Warfarin: PURIXAN may inhibit the anticoagulant effect. (7.2)

**See 17 for PATIENT COUNSELING INFORMATION**  
**Revised: 05/2017**

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

A press-in bottle adapter and two oral dispensing syringes (one 1 mL and one 5 mL) are provided.

The oral dispensing syringe is intended for multiple use: wash the oral dispensing syringe with warm ‘soapy’ water and rinse well; hold the oral dispensing syringe under water and move the plunger up and down several times to make sure the inside of the oral dispensing syringe is clean; ensure the oral dispensing syringe is completely dry before use of the oral dispensing syringe again for dosing; and store the oral dispensing syringe in a hygienic place with the medicine.

Instruct patients to minimize sun exposure due to risk of photosensitivity.

PURIXAN is a cytotoxic drug. Follow special handling and disposal procedures.<sup>1</sup>

## 3. DOSAGE FORMS AND STRENGTHS

Oral Suspension: 2000 mg/100 mL (20 mg/mL) – pink to brown in color.

## 4. CONTRAINDICATIONS

None.

## 5. WARNINGS AND PRECAUTIONS

### 5.1 Myelosuppression

The most consistent, dose-related toxicity of PURIXAN is bone marrow suppression, manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Monitor CBC and adjust the dose of PURIXAN for severe neutropenia and thrombocytopenia.

Evaluate patients with repeated severe myelosuppression for thiopurine S–methyltransferase (TPMT) deficiency. Patients with homozygous-TPMT deficiency require substantial dose reductions of PURIXAN [see *Dosage and Administration (2.1), and Clinical Pharmacology (12.5)*].

Avoid the concurrent use of allopurinol and PURIXAN. Concomitant allopurinol and PURIXAN can result in a significant increase in bone marrow toxicity. Myelosuppression can be exacerbated by coadministration with drugs that inhibit TPMT (e.g., olsalazine, mesalamine, or sulfasalazine) or drugs whose primary or secondary toxicity is myelosuppression [see *Drug Interactions (7.1, 7.3 and 7.4)*].

### 5.2 Hepatotoxicity

Mercaptopurine is hepatotoxic. There are reports of deaths attributed to hepatic necrosis associated with the administration of mercaptopurine. Hepatic injury can occur with any dosage, but seems to occur with greater frequency when the recommended dosage is exceeded. In some patients jaundice has cleared following withdrawal of mercaptopurine and reappeared with rechallenge.

Usually, clinically detectable jaundice appears early in the course of treatment (1 to 2 months). However, jaundice has been reported as early as 1 week and as late as 8 years after the start of treatment with mercaptopurine.

The hepatotoxicity has been associated in some cases with anorexia, diarrhea, jaundice and ascites. Hepatic encephalopathy has occurred.

Monitor serum transaminase levels, alkaline phosphatase, and bilirubin levels at weekly intervals when first beginning therapy and at monthly intervals thereafter. Monitor liver function more frequently in patients who are receiving mercaptopurine with other hepatotoxic drugs or with known pre-existing liver disease. Interrupt PURIXAN in patients with onset of clinical or laboratory evidence of hepatotoxicity.

### 5.3 Immunosuppression

Mercaptopurine is immunosuppressive and may impair the immune response to infectious agents or vaccines. Due to the immunosuppression associated with maintenance chemotherapy for ALL, response to all vaccines may be diminished and there is a risk of infection with live virus vaccines. Consult immunization guidelines for immunocompromised children.

### 5.4 Embryo-Fetal Toxicity

PURIXAN can cause fetal harm when administered to a pregnant woman. Women receiving PURIXAN in the first trimester of pregnancy have an increased incidence of abortion. Adverse embryo-fetal findings were reported in women receiving mercaptopurine after the first trimester of pregnancy and included abortion and stillbirth.

There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to a fetus.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving PURIXAN [see *Use in Specific Populations (8.1)*].

### 5.5 Treatment Related Malignancies

Cases of hepatosplenic T-cell lymphoma have been reported in patients treated with mercaptopurine for inflammatory bowel disease (IBD), an unapproved use. Mercaptopurine is mutagenic in animals and humans, carcinogenic in animals, and may increase the risk of secondary malignancies.

Patients receiving immunosuppressive therapy, including mercaptopurine, are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi’s and non-Kaposi’s) and uterine cervical cancer in situ. The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

A treatment regimen containing multiple immunosuppressants (including thiopurines) should therefore be used with caution as this could lead to lymphoproliferative disorders, some with reported fatalities. A combination of multiple immunosuppressants, given concomitantly increases the risk of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders.

### 5.6 Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) (hemophagocytic lymphohistiocytosis) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (IBD), and there could potentially be an increased susceptibility for developing the condition with the use of mercaptopurine (an unapproved use). If MAS occurs, or is suspected, discontinue mercaptopurine. Monitor for and promptly treat infections such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

### 5.7 Laboratory Tests

Monitor the following laboratory tests in patients receiving PURIXAN: Complete blood counts (CBCs), transaminases, and bilirubin. Evaluate the bone marrow in patients with prolonged or repeated marrow suppression to assess leukemia status and marrow cellularity. Evaluate TPMT status in patients with clinical or laboratory evidence of severe bone marrow toxicity, or repeated episodes of myelosuppression.

## 6. ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the prescribing information:

- Myelosuppression [see *Warnings and Precautions (5.1)*]
- Hepatotoxicity [see *Warnings and Precautions (5.2)*]
- Immunosuppression [see *Warnings and Precautions (5.3)*]
- Embryo-Fetal Toxicity [see *Warnings and Precautions (5.4)*]
- Treatment Related Malignancies [see *Warnings and Precautions (5.5)*]
- Macrophage Activation Syndrome [see *Warnings and Precautions (5.6)*]

### 6.1 Clinical Studies Experience

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.

Based on multicenter cooperative group ALL trials, the most common adverse reaction occurring in > 20% of patients is myelosuppression including anemia, neutropenia, lymphopenia and thrombocytopenia. Adverse reactions occurring 5 to 20 % include anorexia, nausea, vomiting, diarrhea, malaise, and rash. Adverse reactions occurring in < 5 % of patients include urticaria, hyperuricemia, oral lesions, elevated transaminases, hyperbilirubinemia, hyperpigmentation, and pancreatitis. Oral lesions resemble thrush rather than antifolic ulcerations. Delayed or late toxicities include hepatic fibrosis, hyperbilirubinemia, alopecia, pulmonary fibrosis, oligospermia and secondary malignancies [see *Warnings and Precautions (5.1 and 5.2)*].

Drug fever has been reported with PURIXAN. Before attributing fever to PURIXAN, every attempt should be made to exclude more common causes of pyrexia, such as sepsis, in patients with acute leukemia.

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**Instructions for Use**  
**PURIXAN® (pure-ee-zan)**  
(mercaptapurine)  
oral suspension  
20 mg/mL

Read these Instructions for Use before you start taking PURIXAN, and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

**Important information about measuring PURIXAN oral suspension**

- Always use the oral dispensing syringe provided with your PURIXAN oral suspension to make sure you measure the right amount.
- You will be provided:
  - 1 bottle of PURIXAN oral suspension
  - 1 bottle adapter
  - 2 oral dispensing syringes (one 1 mL and one 5 mL)

**If you did not receive an oral dispensing syringe with your PURIXAN oral suspension, ask your pharmacist to give you one.**

**You will also need disposable gloves.**

**Before you use PURIXAN oral suspension for the first time:**

1. Wash your hands well with soap and water before and after administering a dose.
2. Put on disposable gloves before handling PURIXAN.
3. Shake the bottle vigorously for at least 30 seconds to make sure that the medicine is well mixed (See Figure A).
4. Remove the child-resistant bottle cap (see Figure B).
5. Push the ribbed end of the bottle adapter into the neck of the bottle until it is firmly in place. The bottom edge of the adapter should fully contact the top rim of the bottle (See Figure C). Do not remove the adapter from the bottle after it is inserted.

**To prepare a dose of PURIXAN oral suspension:**

6. Hold the bottle upright. Remove the bottle cap by turning in the direction of the arrow (See Figure B).
7. Push the tip of the oral dispensing syringe into the hole in the bottle adapter (See Figure D and Figure E).
8. Turn the bottle upside down (See Figure F).
9. Pull back slowly on the plunger of the oral dispensing syringe to withdraw the prescribed dose of PURIXAN. Pull the plunger back to the mL mark on the syringe that corresponds to the dose prescribed (Figure F). If you are not sure about how much medicine to draw into the oral dispensing syringe, always ask your doctor, pharmacist or nurse for advice.
10. Leave the oral dispensing syringe in the bottle adapter and turn the bottle right-side up. Place the bottle onto a flat surface. Hold the oral dispensing syringe by the barrel and carefully remove it from the adapter. **Do not** hold the oral dispensing syringe by the plunger, because the plunger may come out.
11. Place the tip of the oral dispensing syringe in your mouth and aim the tip toward the inside of your cheek.
12. Gently squirt the PURIXAN oral suspension into your mouth by pushing on the plunger until the oral dispensing syringe is empty. Swallow the medicine.
  - **Do not** forcefully push on the plunger.
  - **Do not** squirt the medicine to the back of your mouth or throat. This may cause you to choke.
13. Remove the oral dispensing syringe from your mouth.
14. Swallow the dose of oral suspension then drink some water, making sure no medicine is left in your mouth.
15. Put the cap back on the bottle with the adapter left in place. Close the cap tightly.
16. Wash the oral dispensing syringe with warm soapy water and rinse well. Hold the oral dispensing syringe under water and move the plunger up and down several times to make sure the inside of the oral dispensing syringe is clean. Let the oral dispensing syringe dry completely before you use it again for dosing. **Do not throw away the oral dispensing syringe after use.**

**What are the ingredients in PURIXAN oral suspension?**

Active ingredient: mercaptopurine

Inactive ingredients: xanthan gum, aspartame, concentrated raspberry juice, sucrose, ethyl parahydroxybenzoate sodium, methyl parahydroxybenzoate sodium, potassium sorbate, sodium hydroxide, and purified water.

**How should I store PURIXAN oral suspension?**

- Store PURIXAN between 59°F to 77°F (15°C to 25°C), in a dry place. Do not store above 25°C.
- Store the oral dispensing syringe in a clean place, with the medicine.
- PURIXAN oral suspension should be used within 8 weeks after opening the bottle. Dispose of (throw away) any unused medicine after 8 weeks.
- Do not use after the expiry date which is stated on the carton and the bottle after ‘EXP’.
- Keep the bottle tightly closed to prevent spoilage of the medicine and reduce the risk of accidental spillage.
- **Keep PURIXAN oral suspension and all medicines out of the reach of children, preferably in a locked cupboard. If a child accidentally takes PURIXAN, it could cause death.** Ask your pharmacist how to dispose of (throw away) PURIXAN that is no longer needed.

**How should I dispose of Purixan?**

- Ask your pharmacist how to dispose of Purixan that is expired or no longer required. Medicines should not be disposed of via wastewater or household waste.

**How do I clean up spillage of Purixan?**

Use appropriate personal protective equipment (disposable gloves and eye protection). Mop up and contain spill material in a compatible container. Wash your hands thoroughly afterwards.

**What do I do if Purixan came into contact with skin, eyes, or clothes?**

- Remove and launder contaminated clothing.
- Wash skin or eyes immediately with water.

Contact with skin or eyes can cause hypersensitive reactions resulting in rash, redness, itching and inflammation. If symptoms appear, seek medical attention. This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by: Nova Laboratories Ltd, Leicester, LE18 4YL, United Kingdom

Manufactured for: Rare Disease Therapeutics, Inc., 2550 Meridian Blvd., Suite 150, Franklin, TN 37067

Part Number: D000764/1

Revised: May 2017

**6.2 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of PURIXAN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include: photosensitivity, hypoglycemia, portal hypertension and pancreatitis.

**7. DRUG INTERACTIONS**

**7.1 Allopurinol**

Avoid concomitant use of PURIXAN and allopurinol. Concomitant use of allopurinol with PURIXAN inhibits the first-pass oxidative metabolism of mercaptopurine by xanthine oxidase, leading to mercaptopurine toxicity (bone marrow suppression, nausea, vomiting) [see *Warnings and Precautions (5.1)*].

**7.2 Warfarin**

Concurrent use of PURIXAN and warfarin may result in decreased anticoagulant effectiveness. Monitor prothrombin time or international normalized ratio (INR) in patients receiving oral anticoagulant therapy with warfarin. Adjustments of the warfarin dose may be necessary in order to maintain the desired level of anticoagulation.

**7.3 Myelosuppressants**

Bone marrow suppression may be increased when PURIXAN is combined with other drugs whose primary or secondary toxicity is myelosuppression. Enhanced marrow suppression has been noted in some patients also receiving trimethoprim-sulfamethoxazole. Monitor CBC and adjust the dose of PURIXAN for severe neutropenia and thrombocytopenia [see *Warnings and Precautions (5.1)*].

**7.4 Aminosaliclyate Derivatives**

Concurrent use of PURIXAN and aminosaliclyate derivatives (e.g., olsalazine, mesalamine, or sulfasalazine) may inhibit the TPMT enzyme, resulting in an increased risk of bone marrow suppression. Should aminosaliclyate derivatives and PURIXAN be coadministered, use the lowest possible doses of each drug and closely monitor the patient for bone marrow suppression [see *Warnings and Precautions (5.1)*].

**8. USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

**Pregnancy Category D [see *Warnings and Precautions (5.4)*].**

**Risk Summary**

PURIXAN can cause fetal harm when administered to a pregnant woman. Women receiving PURIXAN have an increased incidence of abortion and stillbirth. Advise women to avoid becoming pregnant while receiving PURIXAN. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

**Human Data**

Women receiving mercaptopurine in the first trimester of pregnancy have an increased incidence of abortion; the risk of malformation in offspring surviving first trimester exposure is not known. In a series of 28 women receiving mercaptopurine after the first trimester of pregnancy, 3 mothers died prior to delivery, 1 delivered a stillborn child, and 1 aborted; there were no cases of macroscopically abnormal fetuses.

**Animal Data**

Mercaptopurine was embryo-lethal and teratogenic in several animal species (rat, mouse, rabbit, and hamster).

**8.3 Nursing Mothers**

It is not known whether mercaptopurine is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from mercaptopurine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**8.4 Pediatric Use**

The evidence for efficacy of mercaptopurine in children with ALL is derived from the published literature and clinical experience. Cases of symptomatic hypoglycemia have been reported in children with ALL receiving mercaptopurine. Reported cases were in children under the age of six or with a low body mass index.

**8.5 Geriatric Use**

Clinical studies of mercaptopurine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**8.6 Renal Impairment**

No formal clinical or pharmacokinetic studies have been conducted in patients with renal impairment. Starting at the low end of the PURIXAN dosing range, or increasing the dosing interval to 36-48 hours can be considered in patients with baseline renal impairment. Subsequent PURIXAN doses should be adjusted based on efficacy and toxicity [see *Dosage and Administration (2.1)* and *Warnings and Precautions (5.1)*].

**8.7 Hepatic Impairment**

No formal clinical or pharmacokinetic studies have been conducted in patients with hepatic impairment. Mercaptopurine is hepatotoxic. In patients with baseline hepatic impairment, starting at the low end of the PURIXAN dose range should be considered and patients should be monitored for toxicity [see *Dosage and Administration (2.1)* and *Warnings and Precautions (5.1, 5.2)*].

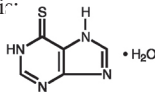
**10. OVERDOSAGE**

Signs and symptoms of mercaptopurine overdose may be immediate (anorexia, nausea, vomiting, and diarrhea); or delayed (myelosuppression, liver dysfunction, and gastroenteritis). Dialysis cannot be expected to clear mercaptopurine. Hemodialysis is thought to be of marginal use due to the rapid intracellular incorporation of mercaptopurine into active metabolites with long persistence. The oral LD<sub>50</sub> of mercaptopurine was determined to be 480mg/kg in the mouse and 425mg/kg in the rat.

There is no known pharmacologic antagonist of mercaptopurine. PURIXAN should be discontinued immediately if unintended toxicity occurs during treatment. If a patient is seen immediately following an accidental overdose of PURIXAN, it may be useful to induce emesis.

**11. DESCRIPTION**

Mercaptopurine, a nucleoside metabolic inhibitor, known chemically as 1,7-dihydro-6H-purine-6-thione monohydrate, is an analogue of the purine bases adenine and hypoxanthine. Mercaptopurine is a yellow, odorless or practically odorless, crystalline powder with a molecular formula of C<sub>4</sub>H<sub>4</sub>N<sub>4</sub>S • H<sub>2</sub>O and a molecular weight of 170.20 as a monohydrate. The structural formula is:



PURIXAN (mercaptopurine) oral suspension is supplied for oral administration and contains 2000 mg/100 mL (20 mg/mL) of mercaptopurine. The suspension also contains the following inactive ingredients: xanthan gum, aspartame, concentrated raspberry juice, sucrose, ethyl parahydroxybenzoate sodium, methyl parahydroxybenzoate sodium, potassium sorbate, sodium hydroxide and purified water. PURIXAN is a pink to brown viscous suspension. In addition, a press-in bottle adapter and two oral dispensing syringes (one 1 mL and one 5 mL) are provided.

**12. CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Mercaptopurine activation occurs via hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) and several enzymes to form 6-thioguanine nucleotides (6-TGNs). Incorporation of 6-TGN into nucleic acids (instead of purine bases) results in cell-cycle arrest and cell death. Mercaptopurine competes with hypoxanthine and guanine for HGPRTase and is itself converted to thioinosinic acid (TIMP). This intracellular nucleotide inhibits several reactions involving inosinic acid (IMP), including the conversion of IMP to xanthylic acid (XMP) and the conversion of IMP to adenylic acid (AMP) via adenylosuccinate (SAMP). In addition, 6-methylthioinosinate

Figure A



Figure B

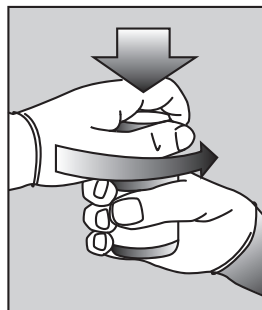


Figure C

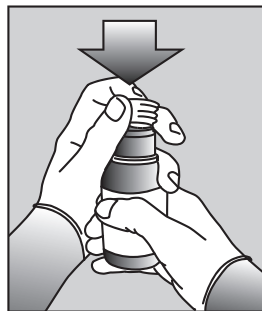


Figure D

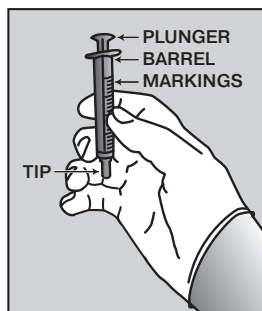


Figure E

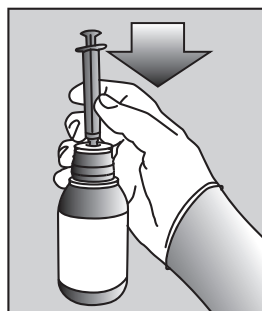
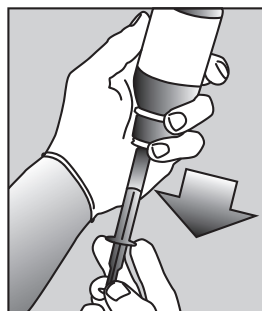


Figure F



(MTIMP) is formed by the methylation of TIMP. Both TIMP and MTIMP have been reported to inhibit glutamine-5-phosphoribosylpyrophosphate amidotransferase, the first enzyme unique to the de novo pathway for purine ribonucleotide synthesis. Experiments indicate that radiolabeled mercaptopurine may be recovered from the DNA in the form of deoxythioguanosine. Some mercaptopurine is converted to nucleotide derivatives of 6-thioguanine (6-TG) by the sequential actions of inosinate (IMP) dehydrogenase and xanthylate (XMP) aminase, converting TIMP to thioguanilic acid (TGMP).

**12.3 Pharmacokinetics**

**Absorption and Bioavailability**

Clinical studies have shown that the absorption of an oral dose of mercaptopurine in humans is incomplete and variable, averaging approximately 50% of the administered dose. The factors influencing absorption are unknown. Following a single 50 mg dose of PURIXAN under fasting conditions the median (range) AUC was 136 h\*ng/mL (74.2-264.8 h\*ng/mL) and Cmax was 95 ng/mL (39.5-204 ng/mL).

**Distribution**

The volume of distribution usually exceeded that of the total body water. There is negligible entry of mercaptopurine into cerebrospinal fluid.

**Metabolism**

Mercaptopurine is inactivated via two major pathways. One is thiol methylation, which is catalyzed by the polymorphic enzyme thiopurine S-methyltransferase (TPMT), to form the inactive metabolite methyl-mercaptopurine. The second inactivation pathway is oxidation, which is catalyzed by xanthine oxidase. The product of oxidation is the inactive metabolite 6-thiouric acid.

**Elimination**

Following administration of PURIXAN, the elimination half-life (t<sub>1/2</sub>) was approximately 2 hours. After oral administration of mercaptopurine, urine contains intact mercaptopurine, thiouric acid (formed by direct oxidation by xanthine oxidase, probably via 6-mercapto-8-hydroxypurine), and a number of 6-methylated thiopurines. In one subject, a total of 46% of the dose could be accounted for in the urine (as parent drug and metabolites) in the first 24 hours.

**12.5 Pharmacogenomics**

TPMT enzyme activity is highly variable in patients because of a genetic polymorphism in the TPMT gene. For Caucasians and African Americans, approximately 0.3% (1:300) of patients have two non-functional alleles (homozygous-deficient) of the TPMT gene and have little or no detectable TPMT activity. Approximately 10% of patients have one TPMT non-functional allele (heterozygous) leading to low or intermediate TPMT activity and 90% of patients have normal TPMT activity with two functional alleles.

Homozygous-deficient patients with little or no detectable TPMT activity, if given usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs predisposing them to mercaptopurine toxicity. Heterozygous patients with low or intermediate TPMT activity accumulate higher concentrations of active 6-TGNs than patients with normal TPMT activity and are more likely to experience mercaptopurine toxicity [see *Warnings and Precautions (5.1)*].

TPMT genotyping or phenotyping (red blood cell TPMT activity) can identify patients who are homozygous deficient or have low or intermediate TPMT activity.

**TPMT Testing**

Genotypic and phenotypic testing of TPMT status are available. Genotypic testing can determine the allelic pattern of a patient. Currently, 3 alleles—TPMT\*2, TPMT\*3A and TPMT\*3C— account for about 95% of individuals with reduced levels of TPMT activity. Individuals homozygous for these alleles are TPMT deficient and those heterozygous for these alleles have variable TPMT (low or intermediate) activity. Phenotypic testing determines the level of thiopurine nucleotides or TPMT activity in erythrocytes and can also be informative. Caution must be used with phenotyping since some coadministered drugs can influence measurement of TPMT activity in blood, and recent blood transfusions will misrepresent a patient’s actual TPMT activity.

**13. NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Mercaptopurine is carcinogenic in animals and humans.

Mercaptopurine causes chromosomal aberrations in animals and humans and induces dominant-lethal mutations in male mice.

Mercaptopurine may impair fertility. In mice, surviving female offspring of mothers who received chronic low doses of mercaptopurine during pregnancy were found sterile, or if they became pregnant, had smaller litters and more dead fetuses as compared to control animals.

**15. REFERENCES**

1. OSHA Hazardous Drugs. OSHA. [Accessed on March 28, 2014, from <http://www.osha.gov/SLTC/hazardousdrugs/index.html>]

**16. HOW SUPPLIED/STORAGE AND HANDLING**

**16.1 How Supplied**

PURIXAN (mercaptopurine) oral suspension 2000 mg/100 mL (20 mg/mL) is a pink to brown viscous liquid supplied in amber glass multiple-dose bottles with a child resistant closure. In addition, a press-in bottle adapter and two oral dispensing syringes (one 1 mL and one 5 mL) are provided.

Each carton NDC 62484-0020-2 contains 1 bottle of PURIXAN NDC 62484-0020-1.

**16.2 Storage and Handling**

- Store PURIXAN between 59° to 77°F (15° to 25°C), in a dry place. Do not store above 25°C.
- Store the oral dispensing syringe in a clean place, with the medicine.
- PURIXAN oral suspension should be used within 8 weeks after opening the bottle. Dispose of (throw away) any unused medicine after 8 weeks.
- Do not use after the expiry date which is stated on the carton and the bottle after ‘EXP’.
- Keep the bottle tightly closed to prevent spoilage of the medicine and reduce the risk of accidental spillage. PURIXAN is a cytotoxic drug. Follow special handling and disposal procedures’.

**17. PATIENT COUNSELING INFORMATION**

Advise the patients and caregivers to read the FDA-approved patient labelling (Patient Information and Instructions for Use).

- **Major Toxicities**
  - Advise patients and caregivers that the major toxicities of PURIXAN are related to myelosuppression, hepatotoxicity, and gastrointestinal toxicity. Advise patients to contact their physician if they experience fever, sore throat, jaundice, nausea, vomiting, signs of local infection, bleeding from any site, or symptoms suggestive of anemia [see *Warnings and Precautions (5.1, 5.2, 5.3)*].
- **Proper Preparation and Administration**
  - Prior to initiation of PURIXAN and on each visit to the clinic, advise patients or caregivers on proper handling, storage, preparation, administration, and disposal and clean-up of accidental spillage of the medication [see *Dosage and Administration (2.3)*]. Advise patients to minimize sun exposure [see *Dosage and Administration (2.3)*].
- **Pregnancy**
  - Advise a female patient of childbearing potential to avoid becoming pregnant [see *Warnings and Precautions (5.4)*].
- Instruct patients and caregivers to keep PURIXAN out of the reach of children.

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Part Number: D000762/1