

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

Dosage and Administration, Maintenance Therapy (2.1) 02/2018
Dosage and Administration, Dosage in Patients with TPMT and/or NUDT15 Deficiency (2.2) 02/2018
Warnings and Precautions, Myelosuppression (5.1) 02/2018

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/m²) 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) or nucleotide diphosphatase (NUDT15) deficiency. Patients with homozygous-TPMT or homozygous-NUDT15 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 and FDA-approved patient labeling.

Revised: 02/2018

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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/m²) as a single daily dose.

After initiating PURIXAN, monitor complete blood counts (CBCs), transaminases, and bilirubin. Maintain ANC at a desirable level by reducing the dose in patients with excessive hematological toxicity. Evaluate the bone marrow in patients with prolonged or repeated marrow suppression to assess leukemia status and marrow cellularity. Evaluate thiopurine S-methyltransferase (TPMT) and nucleotide diphosphatase (NUDT15) status in patients with clinical or laboratory evidence of severe bone marrow toxicity, or repeated episodes of myelosuppression.

2.2 Dosage in Patients with TPMT and/or NUDT15 Deficiency

Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression [*see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)*].

Homozygous deficiency in either TPMT or NUDT15

Patients with homozygous deficiency of either enzyme typically require 10% or less of the standard PURIXAN dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency.

Heterozygous deficiency in TPMT and/or NUDT15

Reduce the PURIXAN dosage based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended mercaptopurine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions.

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.

Prior to dispensing, shake the bottle 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.

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.

PURIXAN is a cytotoxic drug. Follow special handling and disposal procedures.¹

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) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions of PURIXAN [see *Dosage and Administration (2.2) 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.

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, infections, 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.

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 Aminosaliclylate Derivatives

Concurrent use of PURIXAN and aminosaliclylate derivatives (e.g., olsalazine, mesalamine, or sulfasalazine) may inhibit the TPMT enzyme, resulting in an increased risk of bone marrow suppression. Should aminosaliclylate 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

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)*].

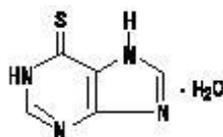
10 OVERDOSAGE

Signs and symptoms of mercaptopurine overdosage 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 LD₅₀ 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 overdosage 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 C₅H₄N₄S·H₂O 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 (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 C_{max} 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 ($t_{1/2}$) 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

Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression [see *Warnings and Precautions (5.1)*]. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage range for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the planned dosage) was as follows: heterozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30-50%; homozygous for either TPMT or NUDT15, 5-10%.

Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity. NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed.

Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood, and blood from recent transfusions will misrepresent a patient's actual TPMT activity [see *Dosage and Administration (2.2)* and *Warnings and Precautions (5.1)*].

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 cap. 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

- PURIXAN is packaged with a child-resistant cap.
- 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 procedures¹.

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)*].
- Pregnancy
 - Advise a female patient of childbearing potential to avoid becoming pregnant [*see Warnings and Precautions (5.4.)*].
- Instruct patients to minimize sun exposure due to risk of photosensitivity.
- Instruct patients and caregivers to keep PURIXAN out of the reach of children.

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PATIENT INFORMATION

PURIXAN® (pure-ee-zan)
(mercaptopurine)
oral suspension

What is PURIXAN?

PURIXAN is a prescription medicine used along with other medicines to treat people with acute lymphoblastic leukemia (ALL).

What should I tell my healthcare provider before taking PURIXAN?

Before you take PURIXAN, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney or liver problems
- have a condition where your body produces too little of the enzyme thiopurine methyltransferase (TPMT) or the enzyme nucleotide diphosphatase (NUDT15).
- have recently received or plan to receive a vaccine
- are pregnant or plan to become pregnant. PURIXAN can harm your unborn baby. You should not become pregnant during treatment with PURIXAN.
- are breastfeeding or plan to breastfeed. It is not known if PURIXAN passes into your breast milk. You and your healthcare provider should decide if you will take PURIXAN or breastfeed. You should not do both.
- **Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take PURIXAN?

- **See the detailed “Instructions for Use” that comes with PURIXAN for information about the right way to measure and take a dose of PURIXAN.**
- Take PURIXAN exactly as your healthcare provider tells you. Do not stop taking PURIXAN or change your dose without talking to your healthcare provider.
- Take PURIXAN by mouth 1 time each day.
- **If Purixan comes into contact with skin, eyes, or clothes?**
 - Remove 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.
- During treatment with PURIXAN, your healthcare provider will do blood tests regularly to check your blood cell counts and liver function, and may change your dose if you have side effects.
- If you miss a dose of PURIXAN, call your healthcare provider for advice.
- If you take too much PURIXAN, call your healthcare provider or go to the nearest emergency room right away.

What should I avoid while taking PURIXAN?

PURIXAN can make your skin more sensitive to sunlight. Protect yourself from sunlight during treatment with PURIXAN.

What are the possible side effects of PURIXAN?

PURIXAN can cause serious side effects, including:

- **Decreased blood cell counts** are common with PURIXAN, but can also be severe. PURIXAN affects your bone marrow and can cause decreased white blood cells, red blood cells, and platelets. Decreased blood cell counts can make you more likely to develop infections, bleeding, or anemia. If you take certain medicines during treatment with PURIXAN, it could make the effects on your bone marrow worse. Tell your healthcare provider if you develop any of the following symptoms during treatment with PURIXAN:
 - fever
 - sore throat
 - cuts or wounds that are red, or swollen, or are draining
 - any bleeding
 - tiredness or weakness
 - shortness of breath
- **Liver problems.** Increases in liver function test results are common with PURIXAN, but you can also develop severe liver problems with PURIXAN that can lead to death. Your healthcare provider may tell you to stop taking

PURIXAN if you develop liver problems. Tell your healthcare provider right away if you develop any of the following symptoms of a liver problem during treatment with PURIXAN:

- decreased appetite
- diarrhea
- nausea or vomiting
- yellowing of your skin or the whites of your eyes
- a build-up of fluid in your stomach-area (ascites)
- **Possible increased risk of other cancers.** Talk with your healthcare provider about your risk of other cancers if you take PURIXAN.

Less common side effects of PURIXAN include: loss of appetite, nausea, vomiting, diarrhea, generally do not feel well, and rash.

Low blood sugar (hypoglycemia) can happen, especially in children under six years of age.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of PURIXAN.

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

How should I store PURIXAN?

- PURIXAN comes in a bottle with a child-resistant cap.
- 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 out of the reach of children, preferably in a locked cupboard. If a child accidentally takes PURIXAN, it could cause death.

How should I dispose of Purixan?

This medicine should not be disposed of in wastewater or household waste. Ask your pharmacist how to dispose of (throw away) PURIXAN that is no longer needed.

General information about the safe and effective use of PURIXAN.

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

What are the ingredients in PURIXAN?

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.

Manufactured by: Nova Laboratories Ltd, Leicester, LE18 4YL, United Kingdom Manufactured for: Rare Disease Therapeutics, Inc., 2550 Meridian Blvd. Suite 150, Franklin, TN 37067 For more information, go to www.purixan-us.com.

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