

DUZALLO- lesinurad and allopurinol tablet, film coated
Ironwood Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

DUZALLO[®] (lesinurad and allopurinol) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: RISK OF ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning

- **Acute renal failure has occurred with lesinurad, one of the components of DUZALLO. (5.1, 6.1)**

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

DUZALLO, a combination of lesinurad, a URAT1 inhibitor, and allopurinol, a xanthine oxidase inhibitor, is indicated for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a medically appropriate daily dose of allopurinol alone. (1)

Limitations of Use:

- DUZALLO is not recommended for the treatment of asymptomatic hyperuricemia. (1.1)

----- **DOSAGE AND ADMINISTRATION** -----

- The recommended dose of DUZALLO is one 200 mg lesinurad/300 mg allopurinol tablet per day (or one 200 mg lesinurad/200 mg allopurinol tablet per day for patients with renal impairment (45 - < 60 mL/min eCLcr) on a medically appropriate dose of 200 mg allopurinol (2.2)).
- Use one tablet of DUZALLO in place of an equivalent portion of the total daily allopurinol dose. The total daily dose of allopurinol should be maintained at the time of initiating DUZALLO. (2.1)
- One tablet of DUZALLO contains the maximum daily lesinurad dose (200 mg). (2.1)
- Do not take more than 1 tablet of DUZALLO per day. (2.1)
- Do not combine DUZALLO with ZURAMPIC[®] (lesinurad). (2.1)
- Use of DUZALLO is not recommended for patients taking daily doses of allopurinol less than 300 mg (or less than 200 mg in patients with moderate renal impairment). (2.1)
- DUZALLO tablets should be taken in the morning with food and water. (2.1)
- Patients should be instructed to stay well hydrated. (2.1)
- Assess renal function before initiating DUZALLO. Do not initiate DUZALLO if eCLcr is below 45 mL/min. (2.2)
- Discontinue DUZALLO if eCLcr persistently falls below 45 mL/min. (2.2)

----- **DOSAGE FORMS AND STRENGTHS** -----

Tablets:

- 200 mg lesinurad/200 mg allopurinol (3)
- 200 mg lesinurad/300 mg allopurinol (3)

----- **CONTRAINDICATIONS** -----

- Severe renal impairment, end-stage renal disease, kidney transplant recipients, or patients on dialysis (4, 8.6)
- Tumor lysis syndrome or Lesch-Nyhan syndrome (4)
- Known hypersensitivity to allopurinol, including previous occurrence of skin rash (5.2)

----- **WARNINGS AND PRECAUTIONS** -----

- **Renal events:** Adverse reactions related to renal function, including acute renal failure, have occurred after initiating lesinurad, one of the components of DUZALLO. A higher incidence has occurred at the 400 mg dose of lesinurad than at the 200 mg dose. Monitor renal function at initiation and during therapy with DUZALLO, particularly in patients with eCLcr below 60 mL/min, and evaluate for signs and symptoms of acute uric acid nephropathy. (5.1)
- **Skin Rash and Hypersensitivity:** DUZALLO, should be discontinued at the first appearance of skin rash or other signs that may indicate an allergic reaction, as allopurinol has been associated with severe hypersensitivity (some resulting in death). (5.2)
- **Hepatotoxicity:** Hepatotoxicity has been reported in patients on allopurinol. Inform patients of warning signs and symptoms of hepatotoxicity. If symptoms develop, liver function evaluation should be performed. (5.3)
- **Cardiovascular events:** Major adverse cardiovascular events were observed with lesinurad; a causal relationship has not

been established. (5.4)

- *Bone Marrow Suppression*: Bone marrow depression affecting one or more cell lines has been reported with allopurinol. (5.5)

----- **ADVERSE REACTIONS** -----

- Most common adverse reactions in 12-month controlled clinical trials (occurring in greater than or equal to 2% of patients treated with lesinurad in combination with a xanthine oxidase inhibitor and more frequently than on xanthine oxidase inhibitor alone) were headache, influenza, blood creatinine increased, and gastroesophageal reflux disease. (6.1)
- The most frequently reported adverse reaction for allopurinol is skin rash. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Ironwood Pharmaceuticals, Inc. at 1-844-374-4793 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **DRUG INTERACTIONS** -----

- *Mercaptopurine or Azathioprine*: Reduce mercaptopurine or azathioprine dose to approximately one-third to one-fourth of the usual dose and closely monitor for therapeutic response and the appearance of toxicity. (5.5, 7.2)
- *Coumarin Anticoagulants*: Carefully monitor prothrombin time. (5.6, 7.2)
- *Moderate Cytochrome P450 2C9 (CYP2C9) Inhibitors*: Use DUZALLO with caution. (7.1)
- *CYP3A Substrates*: Monitor for efficacy of the CYP3A substrate. (7.1)

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

- *Renal impairment*: Not recommended for patients with eCLCr below 45 mL/min. (2.2, 5.1, 8.6)
- *Hepatic impairment*: Not recommended for patients with severe hepatic impairment. (8.7)

See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**.

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF ACUTE RENAL FAILURE

- **Acute renal failure has occurred with lesinurad, one of the components of DUZALLO.**
[see *Warning and Precautions (5.1)*, *Adverse Reactions (6.1)*]

1 INDICATIONS AND USAGE

DUZALLO®, a combination of lesinurad, a uric acid transporter 1 (URAT1) inhibitor, and allopurinol, a xanthine oxidase inhibitor, is indicated for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a medically appropriate daily dose of allopurinol alone [see *Clinical Studies (14)*].

1.1 Limitations of Use

DUZALLO is not recommended for the treatment of asymptomatic hyperuricemia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

DUZALLO tablets are for oral use. DUZALLO should be taken once daily by mouth, in the morning with food and water. Patients should be instructed to stay well hydrated (e.g., 2 liters of liquid per day).

One tablet of DUZALLO contains the maximum daily lesinurad dose (200 mg). Do not take more

than 1 tablet of DUZALLO per day. Do not combine DUZALLO with ZURAMPIC® (lesinurad).

Use of DUZALLO is not recommended for patients taking daily doses of allopurinol less than 300 mg (or less than 200 mg in patients with estimated creatinine clearance [eCLcr] less than 60 mL/min).

Use one tablet of DUZALLO in place of an equivalent portion of the total daily allopurinol dose. The total daily dose of allopurinol should be maintained at the time of initiating DUZALLO.

- For patients who have not achieved target serum uric acid on a medically appropriate dose of allopurinol > 300 mg, DUZALLO may be initiated by using one tablet of DUZALLO in place of an equivalent portion of the total daily allopurinol dose.
- For patients who have not achieved target serum uric acid on a medically appropriate dose of allopurinol of 300 mg, DUZALLO may be initiated by using one tablet of DUZALLO 200 mg lesinurad /300 mg allopurinol daily in place of 300 mg of allopurinol.
- For patients who have not achieved target serum uric acid on a medically appropriate dose of allopurinol of 200 mg, DUZALLO may be initiated by using one tablet of DUZALLO 200 mg lesinurad /200 mg allopurinol daily in place of 200 mg of allopurinol.

For patients currently on ZURAMPIC (lesinurad) in combination with allopurinol, DUZALLO may be initiated by using one tablet of DUZALLO in place of ZURAMPIC (lesinurad) and an equivalent portion of the daily allopurinol dose.

2.2 Patients With Renal Impairment

Patients with decreased renal function require lower doses of allopurinol than those with normal renal function. No dose adjustment is needed for lesinurad in patients with mild or moderate renal impairment (eCLcr of 45 mL/min or greater).

Assessment of renal function is recommended prior to initiation of DUZALLO and periodically thereafter [see *Warnings and Precautions (5.1)*]. DUZALLO should not be initiated in patients with an eCLcr less than 45 mL/min. DUZALLO should be discontinued when eCLcr is persistently less than 45 mL/min [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.6)*]. More frequent renal function monitoring is recommended in patients with an eCLcr below 60 mL/min.

2.3 Gout Flares

Gout flares may occur after initiation of urate-lowering therapy, including DUZALLO, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. For patients not currently taking lesinurad, gout flare prophylaxis is recommended when starting DUZALLO, according to practice guidelines.

If a gout flare occurs during DUZALLO treatment, DUZALLO need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient [see *Patient Counseling Information (17)*].

3 DOSAGE FORMS AND STRENGTHS

DUZALLO is a combination of lesinurad and allopurinol. DUZALLO capsule-shaped tablets are available in the following dosage forms and strengths:

- 200 mg/200 mg tablets are light orange film-coated tablets debossed with "LES200" above "ALO200".
- 200 mg/300 mg tablets are dark orange film-coated tablets debossed with "LES200" above "ALO300".

4 CONTRAINDICATIONS

The use of DUZALLO is contraindicated in the following conditions:

- Severe renal impairment (eCLcr less than 30 mL/min), end-stage renal disease, kidney transplant recipients, or patients on dialysis [see *Use in Specific Populations (8.6)*].
- Tumor lysis syndrome or Lesch-Nyhan syndrome [see *Use in Specific Populations (8.8)*].
- Known hypersensitivity to allopurinol, including previous occurrence of skin rash [see *Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Renal Events

Adverse reactions related to renal function, including acute renal failure, can occur after initiating DUZALLO. Treatment with lesinurad 200 mg in combination with allopurinol was associated with an increased incidence of serum creatinine elevations, most of which were reversible [see *Adverse Reactions (6.1)*]. A higher incidence of serum creatinine elevations and renal-related adverse reactions, including serious adverse reactions of acute renal failure, were observed with lesinurad 400 mg in combination with allopurinol, with the highest incidence when lesinurad was given alone. DUZALLO treatment should be interrupted if serum creatinine is elevated to greater than 2 times the value when lesinurad treatment was initiated. In patients who report symptoms that may indicate acute uric acid nephropathy including flank pain, nausea or vomiting, interrupt treatment and measure serum creatinine promptly. DUZALLO should not be restarted without another explanation for the serum creatinine abnormalities.

DUZALLO should not be initiated in patients with an eCLcr less than 45 mL/min. Renal function should be evaluated prior to initiation of DUZALLO and periodically thereafter, as clinically indicated. More frequent renal function monitoring is recommended in patients with an eCLcr less than 60 mL/min [see *Renal Impairment (8.6)*] or with serum creatinine elevations 1.5 to 2 times the value when lesinurad treatment was initiated.

Some patients with pre-existing renal disease or poor urate clearance have shown a rise in BUN during administration of allopurinol.

5.2 Skin Rash and Hypersensitivity

Skin rash is a frequently reported adverse event in patients taking allopurinol [see *Adverse Reactions (6.2)*]. In some instances, a skin rash may be followed by more severe hypersensitivity reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia including Stevens-Johnson syndrome and toxic epidermal necrolysis. Associated vasculitis and tissue response may be manifested in various ways including hepatitis, renal impairment, seizures, and on rare occasions, death. The HLA-B*5801 allele is a genetic risk marker for severe skin reactions indicative of hypersensitivity to allopurinol.

DUZALLO should be discontinued immediately at the first appearance of skin rash or other signs which may indicate an allergic reaction, and additional medical care should be provided as needed.

Hypersensitivity reactions to allopurinol may be increased in patients with decreased renal function receiving thiazide diuretics and DUZALLO concurrently. For this reason, in this clinical setting, such combinations should be administered with caution and patients should be observed closely.

5.3 Hepatotoxicity

A few cases of reversible clinical hepatotoxicity have been reported in patients taking allopurinol, and in some patients, asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. If anorexia, weight loss, or pruritus develops in patients on DUZALLO, evaluation of liver function should be performed. In patients with pre-existing liver disease, periodic liver function tests are recommended.

5.4 Cardiovascular Events

In clinical trials with lesinurad and allopurinol, major adverse cardiovascular events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were observed [see *Adverse Reactions (6.1)*]. A causal relationship has not been established.

5.5 Bone Marrow Depression

Bone marrow depression has been reported in patients receiving allopurinol, most of whom received concomitant drugs with the potential for causing this reaction. This has occurred as early as six weeks to as long as six years after the initiation of allopurinol therapy. Rarely a patient may develop varying degrees of bone marrow depression, affecting one or more cell lines, while receiving allopurinol alone.

Patients taking allopurinol and mercaptopurine or azathioprine require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of mercaptopurine or azathioprine should be made on the basis of therapeutic response and the appearance of toxic effects. Patients should be closely monitored for therapeutic response and the appearance of toxicity [see *Drug Interaction (7.2)*].

5.6 Increase in Prothrombin Time

It has been reported that allopurinol prolongs the half-life of dicumarol, a coumarin anticoagulant. The prothrombin time should be reassessed periodically in patients receiving coumarin anticoagulants (dicumarol, warfarin) concomitantly with DUZALLO [see *Drug Interaction (7.2)*].

5.7 Drowsiness

Occasional occurrence of drowsiness was reported in patients taking allopurinol. Patients should be alerted to the need for due caution when engaging in activities where alertness is mandatory [see *Patient Counseling Information (17)*].

6 ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections:

- Renal Events [see *Boxed Warning and Warnings and Precautions (5.1)*].
- Skin Rash and Hypersensitivity [see *Warnings and Precautions (5.2)*].
- Hepatotoxicity [see *Warnings and Precautions (5.3)*].
- Cardiovascular Events [see *Warnings and Precautions (5.4)*].
- Bone Marrow Depression [see *Warnings and Precautions (5.5)*].
- Drowsiness [see *Warnings and Precautions (5.7)*].

6.1 Clinical Trials 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 clinical practice.

Lesinurad in Combination With Allopurinol

In 2 randomized, placebo-controlled studies (Studies 1 and 2), a total of 405, 401, and 407 patients with gout were treated with lesinurad 200 mg, lesinurad 400 mg, or placebo, respectively, once daily in combination with allopurinol (200 mg to 900 mg daily) for up to 12 months. The majority of patients in these studies received allopurinol daily doses of 200 mg or 300 mg (average dose of allopurinol in the studies was 310 mg), corresponding to the allopurinol doses contained in DUZALLO. The median duration of treatment with lesinurad in combination with allopurinol was 11.2 months. The mean age of the population was 52 years (range 18-82), and 95% were males. At baseline, 61% of the patient population showed mild or moderate renal impairment (eCLcr less than 90 mL/min) and 81% of patients had at least one co-morbid condition including hypertension (66%), hyperlipidemia (46%), diabetes

(17%), and kidney stones (12%).

Renal Events

Lesinurad causes an increase in renal uric acid excretion, which may lead to renal events including transient increases in serum creatinine, renal-related adverse reactions, and kidney stones. These renal events occurred more frequently in patients receiving lesinurad 400 mg than in patients receiving 200 mg [see *Warnings and Precautions (5.1)*].

The number of patients with serum creatinine elevations in the 12-month placebo-controlled trials in combination with allopurinol is shown in Table 1. Most of these elevations on lesinurad 200 mg in combination with allopurinol and lesinurad 400 mg in combination with allopurinol resolved without treatment interruption (Table 1).

Table 1: Patients With Elevated Serum Creatinine Values in the Placebo-Controlled Clinical Studies With Lesinurad in Combination With Allopurinol

[n (%)]	Placebo + Allopurinol (N=407)	Lesinurad 200 mg + Allopurinol (N=405)	Lesinurad 400 mg + Allopurinol (N=401)
Serum creatinine elevation 1.5 × to < 2.0 × baseline	9 (2.2%)	18 (4.4%)	44 (11.0%)
Resolution of serum creatinine elevations by end of study	6/9 (66.7%)	16/18 (88.9%)	35/44 (79.5%)
Serum creatinine elevation ≥ 2.0 × baseline	0	6 (1.5%)	28 (7.0%)
Resolution of serum creatinine elevations by end of study	N/A	6/6 (100.0%)	21/28 (75.0%)

Renal-related adverse reactions, including blood creatinine increased and renal failure, and nephrolithiasis reported in patients receiving lesinurad 200 mg, lesinurad 400 mg, and placebo in combination with allopurinol are shown in Table 2 [see *Warnings and Precautions (5.1)*]. The incidence of reports of "blood creatinine increased" was higher with lesinurad in combination with allopurinol and was highest with lesinurad 400 mg in combination with allopurinol. Renal-related adverse reactions by baseline renal function category are shown in Table 3 [see *Warnings and Precautions (5.1)*]. Blood creatinine increased occurred more frequently in patients treated with lesinurad 400 mg in combination with allopurinol across baseline renal function categories (Table 3).

Table 2: Incidence of Renal-Related Adverse Reactions and Nephrolithiasis in Placebo-Controlled Clinical Studies With Lesinurad in Combination With Allopurinol

[n (%)]	Placebo + Allopurinol (N=407)	Lesinurad 200 mg + Allopurinol (N=405)	Lesinurad 400 mg + Allopurinol (N=401)
Blood creatinine increased	9 (2.2%)	15 (3.7%)	32 (8.0%)
Renal failure*	7 (1.7%)	4 (1.0%)	14 (3.5%)
Nephrolithiasis	5 (1.2%)	2 (0.5%)	9 (2.2%)

* Renal failure includes the following adverse reactions: renal failure, renal impairment, renal failure chronic, renal failure acute, acute prerenal failure.

Table 3: Incidence of Renal-Related Adverse Reactions by Baseline Renal Function Category in Placebo-Controlled Clinical Studies With Lesinurad in Combination With Allopurinol

n (%)	Placebo + Allopurinol	Lesinurad 200 mg + Allopurinol	Lesinurad 400 mg + Allopurinol
≥ 90 mL/min	n=149	n=163	n=161
Blood creatinine increased	0	5 (3.1%)	6 (3.7%)
Renal failure*	0	2 (1.2%)	6 (3.7%)
≥ 60 - < 90 mL/min	n=176	n=167	n=168
Blood creatinine increased	3 (1.7%)	5 (3.0%)	17 (10.1%)
Renal failure*	4 (2.3%)	1 (0.6%)	6 (3.6%)
≥ 30 - < 60 mL/min	n=78	n=73	n=70
Blood creatinine increased	6 (7.7%)	4 (5.5%)	8 (11.4%)
Renal failure*	3 (3.8%)	1 (1.4%)	2 (2.9%)

* Renal failure includes the following adverse reactions: renal failure, renal impairment, renal failure chronic, renal failure acute, acute prerenal failure.

Renal-related adverse reactions resulted in a similar discontinuation rate on lesinurad 200 mg in combination with allopurinol (1.0%) and allopurinol alone (1.0%) and a higher rate on lesinurad 400 mg in combination with allopurinol (3.2%). Serious renal-related adverse reactions were reported in patients on lesinurad 400 mg in combination with allopurinol (0.7%) and allopurinol alone (0.2%) and in no patients on lesinurad 200 mg in combination with allopurinol during the 12-month controlled period of the studies. Serious renal-related adverse reactions were reported with lesinurad 200 mg and lesinurad 400 mg in combination with allopurinol in the uncontrolled long-term extensions [see *Warnings and Precautions (5.1)*].

Cardiovascular Safety

Cardiovascular events and deaths were adjudicated as Major Adverse Cardiovascular Events (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in the Phase 3 randomized controlled studies of lesinurad in combination with allopurinol. In the randomized controlled studies, the numbers of patients with adjudicated MACE (incidences per 100 patient-years of exposure) were: 2 (0.60) for placebo, 2 (0.61) for lesinurad 200 mg, and 6 (1.85) for lesinurad 400 mg when used in combination with allopurinol.

Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on lesinurad in combination with a xanthine oxidase inhibitor and at least 1% greater than that observed in patients on placebo with a xanthine oxidase inhibitor were identified in the lesinurad development program. The incidence of these adverse reactions in controlled studies with lesinurad 200 mg in combination with allopurinol is summarized in Table 4.

Table 4: Incidence in Controlled Studies With Lesinurad in Combination With Allopurinol of Adverse Reactions Identified in the Lesinurad Development Program

Adverse Reaction	Placebo + Allopurinol (N=407)	Lesinurad 200 mg + Allopurinol (N=405)
Headache	3.2%	4.2%
Influenza	2.9%	4.9%
Gastroesophageal reflux disease	0.5%	3.2%

6.2 Postmarketing Experience

Allopurinol

The following adverse reactions have been identified during post-approval use of allopurinol. 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.

The most frequent adverse reaction to allopurinol is skin rash [see *Warnings and Precautions* (5.2)].

Most Common Adverse Reactions

Gastrointestinal disorders: diarrhea, nausea

Investigations: blood alkaline phosphatase increased, aspartate aminotransferase increased, alanine aminotransferase increased

Skin and subcutaneous tissue disorders: rash, rash maculo-papular

Less Common (<1%) Adverse Reactions

Blood and lymphatic system disorders: ecchymosis, thrombocytopenia, eosinophilia, leukocytosis, leukopenia

Gastrointestinal disorders: vomiting, abdominal pain, gastritis, dyspepsia

General disorders and administration site conditions: pyrexia

Hepatobiliary disorders: hepatitis (including hepatic necrosis and granulomatous hepatitis), hepatomegaly, hyperbilirubinemia, cholestatic jaundice

Musculoskeletal and connective tissue disorders: myopathy, arthralgia

Nervous system disorders: headache, peripheral neuropathy, neuritis, paresthesia, somnolence, ageusia (taste loss)

Renal and urinary disorders: renal failure, azotemia

Respiratory, thoracic and mediastinal disorders: epistaxis

Skin and subcutaneous tissue disorders: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, leukocytoclastic vasculitis, purpura, bullous dermatitis, exfoliative dermatitis, eczema, pruritus, urticaria, alopecia, onycholysis, lichen planus

Vascular disorders: vasculitis necrotizing, vasculitis

Other Uncommon (<1%) Adverse Events

Blood and lymphatic system disorders: aplastic anemia, agranulocytosis, pancytopenia, anemia, hemolytic anemia, reticulocytosis, lymphadenopathy, lymphocytosis

Cardiac disorders: pericarditis, bradycardia

Endocrine disorders: hypercalcemia, gynecomastia

Eye disorders: cataract, retinitis, iritis, conjunctivitis, amblyopia

Gastrointestinal disorders: hemorrhagic pancreatitis, gastrointestinal hemorrhage, stomatitis, salivary gland enlargement, tongue edema

General disorders and administration site conditions: malaise, asthenia, hyperhidrosis

Infections and infestations: pharyngitis, rhinitis

Investigations: prothrombin level decreased

Metabolism and nutrition disorders: hyperlipidemia, decreased appetite

Musculoskeletal and connective tissue disorders: myalgia

Nervous system disorders: optic neuritis, confusional state, dizziness, vertigo, peroneal nerve palsy, amnesia, tinnitus, insomnia

Psychiatric disorders: libido decreased, depression, erectile dysfunction

Renal and urinary disorders: nephritis, hematuria, albuminuria

Reproductive system and breast disorders: infertility male

Respiratory, thoracic and mediastinal disorders: bronchospasm, asthma

Skin and subcutaneous tissue disorders: furuncle, face edema, skin edema

Vascular disorders: peripheral vascular disorder, thrombophlebitis, vasodilatation

7 DRUG INTERACTIONS

No drug interactions studies were conducted with DUZALLO. However, as DUZALLO contains lesinurad and allopurinol, any interactions that have been identified with these agents individually may

occur with DUZALLO. The following interactions have been noted with the individual components of DUZALLO.

7.1 Drug Interactions With Lesinurad

CYP2C9 Inhibitors, CYP2C9 Poor Metabolizers, and CYP2C9 Inducers

Co-administration of lesinurad with inhibitors of CYP2C9, and administration of lesinurad to CYP2C9 poor metabolizers, resulted in increased lesinurad exposure. DUZALLO should be used with caution in patients taking moderate inhibitors of CYP2C9 (e.g., fluconazole, amiodarone), and in CYP2C9 poor metabolizers [see *Clinical Pharmacology* (12.3)].

Lesinurad exposure is decreased when lesinurad is co-administered with moderate inducers of CYP2C9 (e.g., rifampin, carbamazepine), which may decrease the therapeutic effect of DUZALLO [see *Clinical Pharmacology* (12.3)].

CYP3A Substrates

In interaction studies conducted in healthy subjects with lesinurad and CYP3A substrates, lesinurad reduced the plasma concentrations of sildenafil and amlodipine [see *Clinical Pharmacology* (12.3)]. Although there was not a clinically significant interaction with atorvastatin, HMG-CoA reductase inhibitors that are sensitive CYP3A substrates may be affected by co-administration with DUZALLO. The possibility of reduced efficacy of concomitant drugs that are CYP3A substrates should be considered and their efficacy (e.g., blood pressure and cholesterol levels) should be monitored.

Epoxide Hydrolase Inhibitors

In vitro studies suggest that lesinurad is not an inhibitor of epoxide hydrolase; however, inhibitors of epoxide hydrolase (i.e., valproic acid) may interfere with metabolism of lesinurad. DUZALLO should not be administered with inhibitors of epoxide hydrolase.

Hormonal Contraceptives

Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when DUZALLO is co-administered. Females should practice additional methods of contraception and not rely on hormonal contraception alone when taking DUZALLO.

Aspirin

Aspirin at doses higher than 325 mg per day may decrease the efficacy of DUZALLO. Aspirin at doses of 325 mg or less per day (i.e., for cardiovascular protection) does not decrease the efficacy of DUZALLO and can be co-administered with DUZALLO.

7.2 Drug Interactions With Allopurinol

Immunosuppressants/Cytotoxics

Mercaptopurine and azathioprine

Azathioprine is metabolized to mercaptopurine which is inactivated by the action of xanthine oxidase. Since allopurinol is an inhibitor of xanthine oxidase, the activity of azathioprine and mercaptopurine is prolonged. Therefore, during concomitant administration with DUZALLO, the dose of mercaptopurine or azathioprine will require reduction to approximately one-third to one-fourth of the usual dose, and should be closely monitored for therapeutic response and the appearance of toxicity. Subsequent adjustment of doses of mercaptopurine or azathioprine should be made on the basis of therapeutic response and the appearance of toxic effects [see *Warnings & Precautions* (5.5) and *Clinical Pharmacology* (12.3)].

Cyclophosphamide, doxorubicin, bleomycin, procarbazine, mechloroethamine

Enhanced bone marrow suppression by cyclophosphamide and other cytotoxic agents has been reported among patients with neoplastic disease (except leukemia), in the presence of allopurinol. However, in a

well-controlled study of patients with lymphoma on combination therapy, allopurinol did not increase the marrow toxicity of patients treated with cyclophosphamide, doxorubicin, bleomycin, procarbazine, and/or mechlorethamine [see *Warnings and Precautions* (5.5)].

Cyclosporine

Rare reports indicate that cyclosporine levels may be increased during concomitant treatment with allopurinol. Monitoring of cyclosporine levels and possible adjustment of cyclosporine dosage should be considered when cyclosporine and DUZALLO are coadministered.

Dicumarol

There have been reports of prolonged half-life of dicumarol, a coumarin anticoagulant, when coadministered with allopurinol; therefore, patients receiving DUZALLO in addition to dicumarol must be carefully monitored [see *Warnings & Precautions* (5.6)].

Thiazide diuretics

The concomitant use of allopurinol and thiazide diuretics may contribute to the enhancement of allopurinol toxicity in some patients. Although a causal mechanism and a cause-and-effect relationship have not been established, current evidence suggests that renal function should be monitored in patients on thiazide diuretics and allopurinol even in the absence of renal failure, and dosage levels should be even more conservatively adjusted in those patients on such combined therapy if diminished renal function is detected [see *Warnings and Precautions* (5.2)].

Ampicillin/Amoxicillin

An increase in the frequency of skin rash has been reported among patients receiving amoxicillin or ampicillin concurrently with allopurinol compared to patients who are not receiving both drugs. The cause of the association has not been established. [see *Warnings and Precautions* (5.2)].

Chlorpropamide

Plasma half-life of chlorpropamide may be prolonged by allopurinol, since allopurinol and chlorpropamide may compete for excretion in the renal tubule. The risk of hypoglycemia secondary to this mechanism may be increased if allopurinol and chlorpropamide are given concomitantly in the presence of renal insufficiency.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data on use of DUZALLO or lesinurad in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Limited published data on allopurinol use in pregnant women do not demonstrate a clear pattern or increase in frequency of adverse development outcomes.

Animal reproductive toxicity studies have not been conducted with DUZALLO; however, studies were conducted with its individual components [see *Animal Data*]. No teratogenicity or effects on fetal development were observed in embryo-fetal development studies with oral administration of lesinurad to pregnant rats and rabbits during organogenesis at doses that produced maternal exposures up to 45 and 10 times, respectively, the exposure at the maximum recommended human dose (MRHD). No teratogenic or fetotoxic effects were observed in embryo-fetal development studies with orally administered allopurinol to pregnant rats and rabbits during organogenesis at doses approximately 6 times the MRHD in both species. However, intraperitoneal administration of allopurinol to pregnant mice on gestation days 10 or 13, during the period of organogenesis, produced fetal deaths and teratogenic effects at doses 0.8 times the MRHD and higher.

No adverse developmental effects were observed in a pre- and post-natal development study with oral administration of lesinurad to pregnant rats from organogenesis through lactation at a dose approximately 5 times the MRHD.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. 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.

Animal Data

Lesinurad

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-17, lesinurad was not teratogenic and did not affect fetal development or survival at exposures up to approximately 45 times the MRHD (on an AUC basis at maternal oral doses up to 300 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 7-20, lesinurad was not teratogenic and did not affect fetal development at exposures up to approximately 10 times the MRHD (on an AUC basis at maternal oral doses up to 75 mg/kg/day). Severe maternal toxicity, including mortality, was observed in rats and rabbits at exposures equal to or greater than approximately 45 and 4 times the MRHD (on an AUC basis at maternal oral doses of 300 mg/kg/day in rats and 25 mg/kg/day and higher in rabbits) respectively.

In a pre- and post-natal development study in pregnant female rats dosed from gestation day 7 through lactation day 20, lesinurad had no effects on delivery or growth and development of offspring at a dose approximately 5 times the MRHD (on a mg/m² basis at a maternal oral dose of 100 mg/kg/day). In rats, plasma and milk concentrations of lesinurad were approximately equal.

Allopurinol

In embryo-fetal development studies with pregnant rats or rabbits, allopurinol administered during the period of organogenesis (gestation days 8 – 16) was not teratogenic or fetotoxic in either species at doses up to approximately 6 times the MRHD (on a mg/m² basis at maternal oral doses up to 200 mg/kg/day in rats and 100 mg/kg/day in rabbits). However, in an embryo-fetal development study with pregnant mice, single intraperitoneal doses of allopurinol on gestation days 10 or 13 produced significant increases in fetal deaths and teratogenic effects, including external and skeletal malformations, at 0.8 times the MRHD and higher (on a mg/m² basis at maternal intraperitoneal doses of 50 or 100 mg/kg). It is uncertain whether the findings in mice represented a fetal effect or an effect secondary to maternal toxicity.

Allopurinol crossed the placental barrier following oral administration to pregnant pigs and was detected in fetal plasma.

8.2 Lactation

Risk Summary

There is no information regarding the presence of DUZALLO or lesinurad in human milk, the effects on the breastfed infant, or the effects on milk production. Lesinurad was present in the milk of rats [see *Use in Specific Populations (8.1)*]. Based on information from a single case report, allopurinol and its active metabolite, oxypurinol, were detected in the milk of a mother at five weeks postpartum. There was no report of effects of allopurinol on the breastfed infant or on milk production. The effect of allopurinol on the nursing infant is unknown.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUZALLO and any potential adverse effects on the breastfed infant from DUZALLO or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

No dose adjustment is necessary in elderly patients. In a pool of clinical safety and efficacy studies of lesinurad in combination with allopurinol in gout patients, 12% were 65 years and older and 2% were 75 years and older. No overall differences between lesinurad in combination with allopurinol and allopurinol alone in safety and effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

The efficacy and safety of lesinurad in combination with allopurinol were evaluated in studies that included gout patients with mild and moderate renal impairment [see *Adverse Reactions (6.1)* and *Clinical Studies (14)*]. There were no clear differences in safety and effectiveness of lesinurad in combination with allopurinol in patients with mild renal impairment compared to patients with normal renal function. No lesinurad dose adjustment is recommended [see *Dosage and Administration (2.2)*, and *Clinical Studies (14.3)*].

Across all lesinurad and placebo treatment groups, patients with moderate renal impairment had a higher occurrence of renal-related adverse reactions compared to patients with mild renal impairment or normal renal function [see *Adverse Reactions (6.1)*]. The experience with lesinurad in combination with allopurinol in patients with an eCLcr less than 45 mL/min is limited and there was a trend toward lesser efficacy [see *Clinical Studies (14.3)*]. DUZALLO should not be initiated in patients with an eCLcr less than 45 mL/min. No lesinurad dose adjustment is recommended in patients with an eCLcr 45 to less than 60 mL/min, however, more frequent renal function monitoring is recommended. DUZALLO should be discontinued when eCLcr is persistently less than 45 mL/min [see *Dosage and Administration (2.2)* and *Warnings and Precautions (5.1)*].

The efficacy and safety of DUZALLO have not been evaluated in gout patients with severe renal impairment (eCLcr less than 30 mL/min), with end-stage renal disease, or receiving dialysis. DUZALLO is not expected to be effective in these patient populations [see *Contraindications (4)*].

Lesinurad

The pharmacokinetics (PK) of lesinurad were evaluated in studies that included patients with mild (eCLcr 60 to less than 90 mL/min), moderate (eCLcr 30 to less than 60 mL/min), and severe renal impairment (eCLcr less than 30 mL/min). Lesinurad exposure (AUC) increased by 30%, 50-73%, and 113%, respectively, in subjects with mild, moderate, and severe renal impairment [see *Clinical Pharmacology (12.3)*].

Allopurinol

Allopurinol and its metabolites are excreted via the kidney. Impairment of renal function may lead to retention of the drug and its metabolites with consequent prolongation of action. In patients with severely impaired renal function or decreased urate clearance, the half-life of oxypurinol in the plasma is greatly prolonged.

Patients with reduced renal function require lower doses of allopurinol than those with normal renal function [see *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B) [see *Clinical Pharmacology (12.3)*]. Neither DUZALLO nor its individual components have been studied in patients with severe hepatic impairment; DUZALLO is therefore not recommended in these patients [see *Warnings and Precautions (5.3)*].

8.8 Secondary Hyperuricemia

No studies with DUZALLO have been conducted in patients with secondary hyperuricemia (including organ transplant recipients); DUZALLO is contraindicated for use in tumor lysis syndrome or Lesch-Nyhan syndrome, where the rate of uric acid formation is greatly increased [see *Contraindications (4)*].

10 OVERDOSAGE

Lesinurad

Lesinurad was studied in healthy subjects given single doses up to 1600 mg without evidence of dose-limiting toxicities. In case of overdose patients should be managed by symptomatic and supportive care including adequate hydration. The removal of lesinurad by hemodialysis has not been studied.

Allopurinol

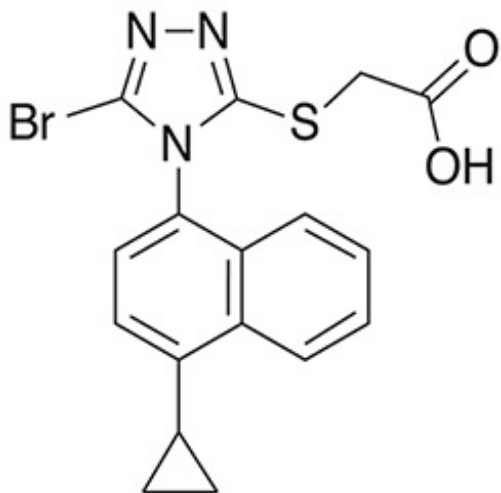
There are published reports of allopurinol overdose in humans, with ingestion of doses up to 22.5 grams. Symptoms and signs including nausea, vomiting, diarrhea and dizziness have been reported. In the management of overdose there is no specific antidote for allopurinol. Both allopurinol and oxypurinol are dialyzable; however, the usefulness of hemodialysis or peritoneal dialysis in the management of an overdose of allopurinol is unknown.

11 DESCRIPTION

DUZALLO (lesinurad and allopurinol) tablets contain 2 oral medications used in the treatment of hyperuricemia: lesinurad and allopurinol. Lesinurad is a URAT1 inhibitor and allopurinol is a xanthine oxidase inhibitor.

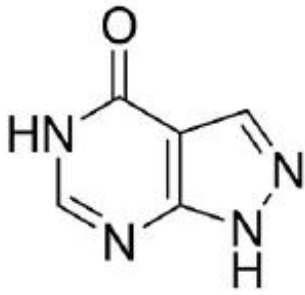
Lesinurad

Lesinurad has the following chemical name: 2-((5-bromo-4-(4-cyclopropyl)naphthalen-1-yl)-4H-1,2,4-triazol-3-yl)thio)acetic acid. The molecular formula is $C_{17}H_{14}BrN_3O_2S$ and the molecular weight is 404.28. The structural formula is:



Allopurinol

Allopurinol has the following chemical name: 1,5-dihydro-4H-Pyrazolo[3,4-*d*]pyrimidin-4-one. The molecular formula is $C_5H_4N_4O$ and the molecular weight is 136.11. The structural formula is:



DUZALLO

DUZALLO is available as a light orange film-coated tablet containing 200 mg of lesinurad and 200 mg of allopurinol or a dark orange film-coated tablet containing 200 mg of lesinurad and 300 mg of allopurinol. The capsule-shaped tablets include the following inactive ingredients: crospovidone, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: hypromellose, iron oxide red, iron oxide yellow, titanium dioxide, and triacetin. DUZALLO 200/200 mg tablets are coated with Opadry orange and 200/300 mg tablets are coated with Opadry beige.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DUZALLO combines two medications with complementary mechanisms of action for treatment of hyperuricemia associated with gout: lesinurad, a uric acid reabsorption inhibitor, and allopurinol, a xanthine oxidase inhibitor. DUZALLO lowers serum uric acid levels by increasing excretion and inhibiting production of uric acid.

Lesinurad

Lesinurad reduces serum uric acid levels by inhibiting the function of transporter proteins involved in uric acid reabsorption in the kidney. Lesinurad inhibited the function of two apical transporters responsible for uric acid reabsorption, uric acid transporter 1 (URAT1) and organic anion transporter 4 (OAT4), with IC_{50} values of 7.3 and 3.7 μ M, respectively. URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. OAT4 is a uric acid transporter associated with diuretic-induced hyperuricemia. Lesinurad does not interact with the uric acid reabsorption transporter SLC2A9 (Glut9), located on the basolateral membrane of the proximal tubule cell.

Allopurinol

Allopurinol acts on purine catabolism, without disrupting the biosynthesis of purines. It reduces the production of uric acid by inhibiting the biochemical reactions immediately preceding its formation. Allopurinol is a structural analogue of the natural purine base, hypoxanthine. It is an inhibitor of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid, the end product of purine metabolism in humans. Allopurinol is metabolized to the corresponding xanthine analogue, oxypurinol (alloxanthine), which also is an inhibitor of xanthine oxidase.

Reutilization of both hypoxanthine and xanthine for nucleotide and nucleic acid synthesis is markedly enhanced when their oxidations are inhibited by allopurinol and oxypurinol. This reutilization does not disrupt normal nucleic acid anabolism because feedback inhibition is an integral part of purine biosynthesis. As a result of xanthine oxidase inhibition, the serum concentration of hypoxanthine plus xanthine in patients receiving allopurinol for treatment of hyperuricemia is usually in the range of 0.3 to 0.4 mg/dL compared to a normal level of approximately 0.15 mg/dL. A maximum of 0.9 mg/dL of these oxypurines has been reported when the serum urate was lowered to less than 2 mg/dL by high doses of allopurinol. These values are far below the saturation levels at which point their precipitation would be

expected to occur (above 7 mg/dL).

12.2 Pharmacodynamics

Effects on Serum Uric Acid and Urinary Excretion of Uric Acid

Lesinurad

In gout patients, lesinurad lowered serum uric acid levels and increased renal clearance and fractional excretion of uric acid. Following single and multiple oral doses of lesinurad to gout patients, dose-dependent decreases in serum uric acid levels and increases in urinary uric acid excretion were observed.

Allopurinol

Allopurinol reduces both the serum and urinary uric acid levels by inhibiting the formation of uric acid.

Effect on Cardiac Repolarization

Lesinurad

The effect of lesinurad on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy subjects and gout patients. Lesinurad at doses up to 1600 mg did not demonstrate an effect on the QTc interval.

Allopurinol

The effect of allopurinol on cardiac repolarization has not been evaluated.

12.3 Pharmacokinetics

DUZALLO

After the administration of DUZALLO with a high-fat breakfast in healthy subjects, the exposure (AUC) for lesinurad and allopurinol were comparable to the fasted state. Compared to the fasted state, the fed state resulted in 46% and 18% reductions and 2.5 hours and 1.75 hours delays, in the peak (C_{max}) concentrations of lesinurad and allopurinol, respectively. This effect of food is not considered to be clinically meaningful. Oxypurinol C_{max} and AUC were similar in the fed and fasted states.

Absorption

Lesinurad

The absolute bioavailability of lesinurad as monotherapy is approximately 100%. Lesinurad is rapidly absorbed after oral administration. Following administration of a single dose of a lesinurad tablet in either fed or fasted state, C_{max} was attained within 1 to 4 hours. C_{max} and AUC exposures of lesinurad increased proportionally with single doses of lesinurad from 5 to 1200 mg. Administration with a high-fat meal (800 to 1000 calories with 50% of calories being derived from fat content) decreases C_{max} by up to 18% but does not alter AUC as compared with fasted state. In clinical trials, lesinurad was administered with food.

Allopurinol

Allopurinol is approximately 90% absorbed from the gastrointestinal tract. Peak plasma levels generally occur at 1.5 hours and 4.5 hours for allopurinol and oxypurinol, respectively. After a single oral dose of 300 mg allopurinol, maximum plasma levels of about 3 mcg/mL of allopurinol and 6.5 mcg/mL of oxypurinol are produced.

Distribution

Lesinurad

Lesinurad is extensively bound to proteins in plasma (greater than 98%), mainly to albumin. Plasma protein binding of lesinurad is not meaningfully altered in patients with renal or hepatic impairment. The

mean steady state volume of distribution of lesinurad was approximately 20 L following intravenous dosing of lesinurad.

Elimination

Lesinurad

The elimination half-life ($t_{1/2}$) of lesinurad is approximately 5 hours. Lesinurad does not accumulate following multiple doses. The total body clearance is approximately 6 L/hr.

Allopurinol

Because of its rapid oxidation to oxypurinol and a renal clearance rate approximately that of glomerular filtration rate, allopurinol has a plasma half-life of about 1 to 2 hours. Oxypurinol, however, has a longer plasma elimination half-life (approximately 26 hours) and therefore effective xanthine oxidase inhibition is maintained over a 24-hour period with single daily doses of allopurinol. Whereas allopurinol is cleared essentially by glomerular filtration, oxypurinol is reabsorbed in the kidney tubules in a manner similar to the reabsorption of uric acid.

Metabolism

Lesinurad

Lesinurad undergoes oxidative metabolism mainly via the polymorphic cytochrome P450 CYP2C9 enzyme. Plasma exposure of metabolites is minimal (<10% of unchanged lesinurad). Metabolites are not known to contribute to the uric acid lowering effects of lesinurad. A transient oxide metabolite is rapidly eliminated by microsomal epoxide hydrolase in the liver and not detected in plasma.

Patients who are CYP2C9 poor metabolizers are deficient in CYP2C9 enzyme activity. A cross-study pharmacogenomic analysis assessed the association between CYP2C9 polymorphism and lesinurad exposure in patients receiving single or multiple doses of lesinurad at 200 mg, 400 mg or 600 mg. At the 400 mg dose, lesinurad exposure was approximately 1.8-fold higher in CYP2C9 poor metabolizers (i.e., subjects with CYP2C9 *2/*2 [N=1], and *3/*3 [N=1] genotype) compared to CYP2C9 extensive metabolizers (i.e., CYP2C9 *1/*1 [N=41] genotype). Use with caution in CYP2C9 poor metabolizers, and in patients taking moderate inhibitors of CYP2C9 [see *Drug Interactions (7.1)*].

Allopurinol

Allopurinol is metabolized to the corresponding xanthine analogue, oxypurinol (alloxanthine), which also is an inhibitor of xanthine oxidase.

Excretion

Lesinurad

Within 7 days following single dosing of radiolabeled lesinurad, 63% of administered radioactive dose was recovered in urine and 32% of administered radioactive dose was recovered in feces. Most of the radioactivity recovered in urine (> 60% of dose) occurred in the first 24 hours. Unchanged lesinurad in urine accounted for approximately 30% of the dose.

Allopurinol

Approximately 20% of the ingested allopurinol is excreted in the feces. The remainder is primarily metabolized to oxypurinol.

SPECIFIC POPULATIONS

Renal Impairment

A dedicated renal impairment study was not conducted with DUZALLO.

Lesinurad

Two dedicated studies were performed to assess pharmacokinetics (PK) of lesinurad in renal

impairment (classified using the Cockcroft-Gault formula) subjects. In both studies, C_{max} was comparable in renal impairment subjects compared to healthy subjects. Study 1 was a single-dose, open-label study evaluating the PK of lesinurad 200 mg in subjects with mild (eCLcr 60 to less than 90 mL/min) and moderate renal impairment (eCLcr 30 to less than 60 mL/min) compared to healthy subjects. Compared to healthy subjects (N=6; eCLcr greater than or equal to 90 mL/min), plasma AUC of lesinurad was increased by approximately 30% and 73% in subjects with mild (N=8) and moderate (N=10) renal impairment, respectively. Study 2 was a single-dose, open-label study evaluating the PK of lesinurad 400 mg in subjects with moderate and severe renal impairment (eCLcr less than 30 mL/min) compared to healthy subjects. Compared to healthy subjects (N=6), plasma AUC of lesinurad was increased by approximately 50% and 113% in subjects with moderate (N=6) and severe (N=6) renal impairment, respectively.

Allopurinol

Allopurinol and its metabolites are primarily eliminated by the kidney. Impairment of renal function may lead to retention of the drug and its metabolites with consequent prolongation of action. Patients with reduced renal function require lower doses of allopurinol than those with normal renal function.

Hepatic Impairment

A dedicated hepatic impairment study was not conducted with DUZALLO.

Lesinurad

Following administration of a single dose of lesinurad at 400 mg in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, lesinurad C_{max} was comparable and lesinurad AUC was 7% and 33% higher, respectively, compared to individuals with normal hepatic function. There is no clinical experience in patients with severe (Child-Pugh class C) hepatic impairment.

Allopurinol

No information is available in patients with hepatic impairment [see *Warnings and Precautions (5.3)*].

Effect of Age, Gender, Race and Ethnicity on Pharmacokinetics

Lesinurad

Based on the population PK analysis, age, gender, race and ethnicity do not have a clinically meaningful effect on the PK of lesinurad [see *Use in Specific Populations (8.5)*].

Allopurinol

No information is available for age, gender, race, or ethnicity effects on the PK of allopurinol.

Pediatric Use

Lesinurad

Studies characterizing the PK of lesinurad in pediatric patients have not been conducted.

Allopurinol

No data on the PK of allopurinol in pediatric patients are available.

Drug-Drug Interactions

Pharmacokinetic drug interaction studies with DUZALLO have not been performed; however, such studies have been conducted with the individual components lesinurad and allopurinol.

Lesinurad

Based on *in vitro* data, lesinurad is a substrate for CYP2C9, OAT1 and OAT3; however, no clinical studies have been conducted with OAT1 and OAT3 inhibitors (e.g., probenecid).

Effects of Other Drugs on Lesinurad

Figure 1 shows the effect of co-administered drugs on the PK of lesinurad.

Figure 1: Effect of Co-Administered Drugs on the Pharmacokinetics of Lesinurad

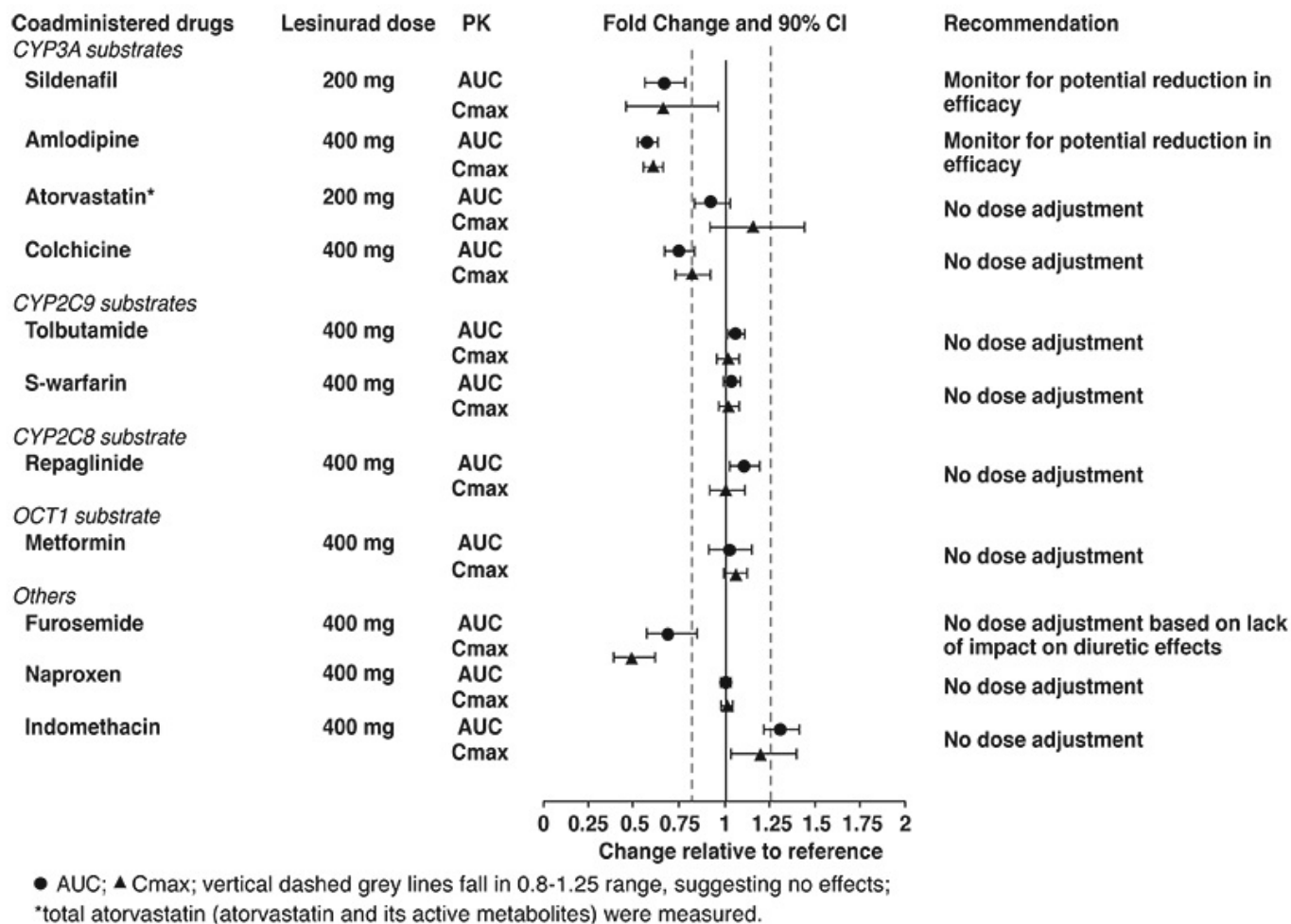
Effects of Lesinurad on Other Drugs

Lesinurad is a weak inducer of CYP3A and has no relevant effect on any other CYP enzyme for induction (CYP1A2, CYP2C8, CYP2C9, CYP2B6, or CYP2C19) or inhibition (CYP1A2, CYP2B6, CYP2D6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4).

Based on *in vitro* studies, lesinurad is an inhibitor of OATP1B1, OCT1, OAT1, and OAT3; however, lesinurad is not an *in vivo* inhibitor of these transporters. *In vivo* drug interaction studies indicate that lesinurad does not decrease the renal clearance of furosemide (substrate of OAT1/3), or affect the exposure of atorvastatin (substrate of OATP1B1) or metformin (substrate of OCT1). Based on *in vitro* studies, lesinurad has no relevant effect on P-glycoprotein.

Figure 2 shows the effect of lesinurad on co-administered drugs.

Figure 2: Effect of Lesinurad on the Pharmacokinetics of Coadministered Drugs



Effect of Allopurinol on Mercaptopurine

Allopurinol inhibits the enzymatic oxidation of mercaptopurine, the sulfur-containing analogue of hypoxanthine, to 6-thiouric acid. This oxidation, which is catalyzed by xanthine oxidase, inactivates mercaptopurine. Hence, the inhibition of such oxidation by allopurinol may result in as much as a 75% reduction in the therapeutic dose requirement of mercaptopurine when the two compounds are given together.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with DUZALLO; however, studies were conducted with its individual components, lesinurad and allopurinol, as described below.

Lesinurad

The carcinogenic potential of lesinurad was evaluated in a 2-year study conducted in Sprague-Dawley rats and a 26-week study in TgRasH2 mice. No evidence of tumorigenicity was observed in male or female rats at oral doses up to 200 mg/kg/day (approximately 35 times the MRHD on an AUC basis). No evidence of tumorigenicity was observed in TgRasH2 mice at oral doses up to 125 and 250 mg/kg/day in male and female mice, respectively.

Lesinurad tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* rat bone marrow micronucleus assay.

Fertility and reproductive performance were unaffected in male or female rats that received lesinurad at oral doses up to 300 mg/kg/day (approximately 15 times the MRHD on a mg/m² basis).

Allopurinol

No evidence of tumorigenicity was observed in male or female mice or rats that received oral allopurinol for the majority of their life spans (greater than 88 weeks) at doses up to 20 mg/kg/day (0.3 and 0.6 times the MRHD on a mg/m² basis in mice and rats respectively).

Allopurinol tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* mouse lymphoma assay, and *in vivo* rat bone marrow micronucleus assay.

Oral allopurinol doses of 20 mg/kg/day had no effect on male or female fertility in rats or rabbits (approximately 0.6 or 1.3 times the MRHD on a mg/m² basis, respectively).

14 CLINICAL STUDIES

Lesinurad in combination with allopurinol has been studied in hyperuricemic gout patients who have not achieved target serum uric acid levels with allopurinol alone.

There have been no phase 3 clinical trials with DUZALLO. Bioequivalence of DUZALLO to co-administered lesinurad and allopurinol was demonstrated, and efficacy of the combination of allopurinol and lesinurad has been demonstrated in two phase 3 studies (Study 1 and 2).

14.1 Lesinurad Add-On to Allopurinol in Inadequate Responders

Both studies were 12-month multicenter, randomized, double-blind, placebo-controlled clinical studies in adult patients with hyperuricemia and gout. Patients received prophylaxis for gout flares with colchicine or non-steroidal anti-inflammatory drugs (NSAIDs) during the first 5 months of study treatment. Lesinurad 200 mg and 400 mg once daily in combination with allopurinol were studied. Lesinurad 200 mg is the only recommended lesinurad dose, and is the dose combined with allopurinol in DUZALLO.

Study 1 and Study 2 enrolled patients with gout who were on a stable dose of allopurinol of at least 300 mg (or 200 mg for moderate renal impairment), had a serum uric acid > 6.5 mg/dL, and reported at least 2 gout flares in the prior 12 months. Mean years since gout diagnosis were 12 years. More than half of the patients (61%) had mild or moderate renal impairment and 19% of the patients had tophi. Patients were randomized 1:1:1 to receive lesinurad 200 mg, lesinurad 400 mg, or placebo once daily; all were to continue on their stable allopurinol dose. The majority of patients in these studies received daily allopurinol doses of 200 mg or 300 mg, corresponding to the allopurinol doses contained in DUZALLO. The average dose of allopurinol in the studies was 310 mg (range: 200-900 mg).

As shown in Table 5, lesinurad 200 mg in combination with allopurinol was superior to allopurinol alone in lowering serum uric acid to less than 6 mg/dL at Month 6.

Table 5: Proportion of Patients Achieving Target Serum Uric Acid Levels (< 6 mg/dL) in Two Studies of Lesinurad in Combination With Allopurinol

Study	Timepoint	Patients Achieving Serum Uric Acid Target		Difference of Proportion (95% C.I.)
		Placebo + Allopurinol	Lesinurad 200 mg + Allopurinol	
Study 1 (N=402*)	Month 6	28%	54%	0.26 (0.17, 0.36)
Study 2 (N=410*)	Month 6	23%	55%	0.32 (0.23, 0.41)

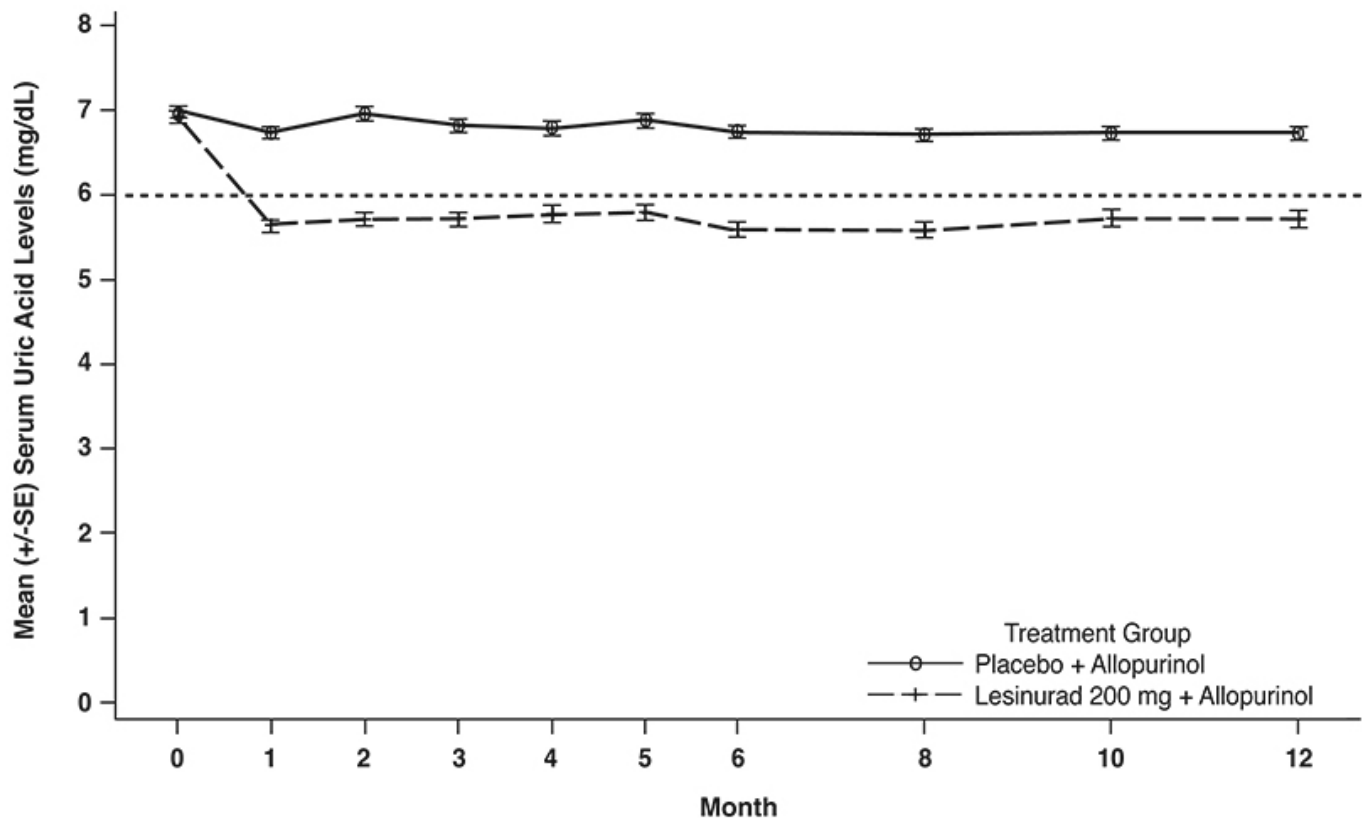
* Number of patients in the 2 treatment groups shown. Number of patients in all 3 treatment groups

N=603 for Study 1 and N=610 for Study 2.

The estimated effect of lesinurad 200 mg on serum uric acid in the subgroup of patients taking thiazide diuretics at baseline was similar to the estimated effect in the overall population. The estimated effect was also similar in the subgroup of patients taking low-dose aspirin at baseline.

As shown in Figure 3, reduction in average serum uric acid levels to < 6 mg/dL was noted for lesinurad 200 mg in combination with allopurinol at the Month 1 visit and was maintained throughout the 12-month studies.

Figure 3: Mean Serum Uric Acid Levels Over Time in Pooled Clinical Studies With Lesinurad in Combination With Allopurinol (Study 1 and Study 2)



14.2 Gout Flares

In Study 1 and Study 2, the rates of gout flare requiring treatment from the end of Month 6 to the end of Month 12 were not statistically different between lesinurad 200 mg in combination with allopurinol compared with allopurinol alone.

14.3 Use in Patients With Renal Impairment

The estimated differences between lesinurad and placebo in the proportions of patients achieving target serum uric acid levels in the renal impairment subgroups were largely consistent with the results in the overall population in the studies. However, there were limited data in patients with eCLcr less than 45 mL/min and there was a trend toward decreasing magnitude of effect with decreasing renal function. Based on integrated data from Study 1 and Study 2, the estimated difference between lesinurad 200 mg in combination with allopurinol and allopurinol alone in the proportion achieving serum uric acid < 6.0 mg/dL at Month 6 was 10% (95% CI: -17, 37) in those with eCLcr less than 45 mL/min as compared with 27% (95% CI: 9, 45) in the 45 to less than 60 mL/min subgroup and 30% (95% CI: 23, 37) in the 60 mL/min or greater subgroup.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DUZALLO tablets have markings on one side, are plain on the reverse side and are available in the strengths and packages listed in Table 6.

Table 6: DUZALLO Tablet Presentations

Tablet Strength (Lesinurad/Allopurinol)	Capsule- Shaped, Film- Coated, Tablet	Tablet Markings	Pack Size	NDC Code
200/200 mg	Light orange film-coated tablet	Debossed with "LES200" above "ALO200"	Bottle of 5 tablets	70785-021-05
			Bottle of 30 tablets	70785-021-30
			Bottle of 90 tablets	70785-021-90
200/300 mg	Dark orange film-coated tablet	Debossed with "LES200" above "ALO300"	Bottle of 5 tablets	70785-022-05
			Bottle of 30 tablets	70785-022-30
			Bottle of 90 tablets	70785-022-90

16.2 Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Administration

Advise patients:

- To take one tablet of DUZALLO in the morning with food and water.
- Not to take a missed dose of DUZALLO later in the day, but to wait to take DUZALLO on the next day, and not to double the dose.
- Not to take DUZALLO with ZURAMPIC (lesinurad).
- To stay well hydrated (e.g., 2 liters of liquid per day).

Renal Events

Inform patients that renal events including transient increases in blood creatinine level and acute renal failure have occurred in some patients who take DUZALLO. Advise patients that periodic monitoring of blood creatinine levels is recommended [see *Warnings and Precautions (5.1)*].

Serious Skin Reactions

Inform patients that DUZALLO may increase the risk of serious skin side effects such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching and should ask for medical advice when observing any indicative signs or symptoms. Advise patients to stop the drug immediately if they develop any type of rash and seek

medical attention [see *Warnings and Precautions (5.2)*].

Gout Flares

Inform patients that gout flares may occur after initiation of DUZALLO and of the importance of taking gout flare prophylaxis medication to help prevent gout flares. Advise patients not to discontinue DUZALLO if a gout flare occurs during treatment [see *Dosage and Administration (2.3)*].

Concomitant Use with Other Medications

Inform patients that use of DUZALLO may increase the risks associated with taking other medications (i.e., coumarin anticoagulants, mercaptopurine, azathioprine and thiazide diuretics) and they should follow the instructions of their healthcare provider [see *Warnings and Precautions (5.5, 5.6)*, *Drug Interactions (7)*].

Ability to Perform Complex Tasks

Patients should be informed that drowsiness has been reported in patients taking allopurinol. Patients should be alerted to the need for due caution when engaging in activities where alertness is mandatory [see *Warnings and Precautions (5.7)*].

Manufactured for: Ironwood Pharmaceuticals, Inc., Cambridge, MA 02142

By: AstraZeneca AB, SE-151 85 Sodertalje, Sweden

Product of Sweden

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MEDICATION GUIDE
DUZALLO[®] (Dew-ZAL-oh)
(lesinurad and allopurinol)
tablets, for oral use

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

DUZALLO can cause serious side effects, including:

- **Kidney problems.** Some people taking DUZALLO may have kidney problems such as a sudden decrease in kidney function (acute kidney failure). Your healthcare provider may do blood tests to check your kidneys while you are taking DUZALLO.
- **Serious skin rash and serious allergic reactions.** Severe and potentially life-threatening allergic reactions and skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis and exfoliative dermatitis have been reported in some people taking allopurinol, one of the components of DUZALLO. **Stop taking DUZALLO and get emergency medical help if you have any of the following symptoms:**
 - skin rash; blistering of the skin, mouth, nose, and genitals
 - joint pain; swollen glands
 - painful red or purple skin that looks burned and peels off
 - red, painful, watery eyes; persistent itching; hives
 - fever

See "**What are the possible side effects of DUZALLO?**" for more information about side effects.

What is DUZALLO?

- DUZALLO is a prescription medicine that contains 2 medicines, a URAT1 inhibitor called lesinurad and a xanthine oxidase inhibitor called allopurinol.
- DUZALLO is used to lower uric acid levels in the blood in people with gout, when allopurinol alone has not worked well enough.

It is not known if DUZALLO is safe and effective in children under 18 years of age.

Do not take DUZALLO if you have:

- severe kidney problems, received a kidney transplant or you are on dialysis
- a fast breakdown of cancer cells that can lead to high uric acid (Tumor lysis syndrome)
- a rare inherited condition that causes too much uric acid in the blood (Lesch-Nyhan syndrome)
- had a skin rash or other allergic reaction after taking allopurinol

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

- have kidney or liver problems.
- are pregnant or plan to become pregnant. It is not known if DUZALLO will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Allopurinol can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take DUZALLO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. DUZALLO may affect the way other medicines work, and other medicines may affect how DUZALLO works.

Especially tell your healthcare provider if you take:

- certain medicines that lower your immune system including mercaptopurine and azathioprine
- blood thinner medicines
- medicines for heart conditions or high blood pressure
- medicines for high blood cholesterol
- antifungals and antibiotics
- valproic acid
- aspirin
- other medicines for gout
- hormonal contraceptives. Women who use birth control medicines containing hormones to prevent pregnancy (birth control pills, skin patches, implants, and certain IUDs) should use a back-up method of birth control during treatment with DUZALLO.

Ask your healthcare provider or pharmacist if you are not sure if you take any of these medicines. Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take DUZALLO?

- Take DUZALLO exactly as your healthcare provider tells you to take it.
- Take 1 DUZALLO tablet each day in the morning. Do not take more than 1 DUZALLO tablet each day.
- **Do not** take DUZALLO with ZURAMPIC[®] (lesinurad).
- Take DUZALLO with food and water.
- Drink 2 liters (68 ounces) of fluid each day to stay hydrated.
- If you miss a dose of DUZALLO in the morning, do not take DUZALLO later in the day. Wait and take your next dose of 1 DUZALLO tablet the next morning. Do not double your dose of DUZALLO.
- Your gout may get worse (flare up) when you first start taking DUZALLO. Do not stop taking DUZALLO even if you have a flare up. Your healthcare provider may give you other medicines to help prevent your gout flare ups.

What should I avoid while taking DUZALLO?

- Avoid becoming dehydrated while taking DUZALLO.
- DUZALLO can cause you to be drowsy. Do not drive, use machinery, or do other dangerous activities until you know how DUZALLO affects you.

What are the possible side effects of DUZALLO?

DUZALLO may cause serious side effects including:

- See "**What is the most important information I should know about DUZALLO?**".
- **Liver problems.** Liver problems can happen in people who take DUZALLO. Call your healthcare provider if you have any of the following symptoms:
 - loss of appetite
 - weight loss
 - feeling very tired
 - nausea or vomiting
 - yellowing of your skin or the white part of your eyes
 - itching
 - dark or brown (tea-colored) urine
 - pain on the upper right side of your stomach
- **Heart problems.** People who take DUZALLO can have serious heart problems including heart attack and stroke. It is not known that DUZALLO causes these problems.
- **Blood problems.** DUZALLO can affect your bone marrow and cause low red blood cells, white blood cells and platelets. If your blood cell counts become very low, you can get infections or have bleeding problems. Taking DUZALLO with certain other medicines can increase your chance of having blood problems.

The most common side effects of DUZALLO include:

- headache
- flu
- higher levels of blood creatinine (a measure of kidney function)
- heartburn (acid reflux)
- skin rash
- nausea
- diarrhea

Tell your healthcare provider if you have any side effect that bothers you, or that does not go away. These are not all of the possible side effects of DUZALLO. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store DUZALLO?

- Store DUZALLO at room temperature between 68°F and 77°F (20°C to 25°C).

Keep DUZALLO and all medicines out of the reach of children.

General Information about the safe and effective use of DUZALLO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DUZALLO for a condition for which it was not prescribed. Do not give DUZALLO to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about DUZALLO that is written for health professionals.

What are the ingredients in DUZALLO?

Active ingredients: lesinurad and allopurinol

Inactive ingredients: crospovidone, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, iron oxide red, iron oxide yellow, titanium dioxide, and triacetin. DUZALLO 200/200 mg tablets are coated with Opadry orange and DUZALLO 200/300 mg tablets are coated with Opadry beige.

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By: AstraZeneca AB, SE-151 85 Sodertalje, Sweden.

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For more information, go to www.DUZALLO.com or call 1-844-374-4793.

PRINCIPAL DISPLAY PANEL - 200 mg/200 mg Tablet Bottle Label

NDC 70785-021-90

90 Tablets

DUZALLO™

lesinurad/allopurinol
tablets

200 mg/200 mg

**Dispense the accompanying
Medication Guide to each patient.**

Rx only

Ironwood®

NDC 70785-021-90 **90 Tablets**

 **DUZALLO™**
lesinurad/allopurinol
tablets

200 mg / 200 mg

Dispense the accompanying
Medication Guide to each patient.

Rx only

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Cambridge, MA 02142
By: AstraZeneca AB, SE-151 85 Södertälje, Sweden
Product of Sweden

GTIN 00370785021904 00-00000

AREA RESERVED
FOR VARIABLE DATA

Usual Adult Dosage: See full prescribing information.
Store at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]
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PRINCIPAL DISPLAY PANEL - 200 mg/300 mg Tablet Bottle Label

NDC 70785-022-90

90 Tablets

DUZALLO™

lesinurad/allopurinol
tablets

200 mg/300 mg

**Dispense the accompanying
Medication Guide to each patient.**

Rx only

Ironwood®

Manufactured for: Ironwood Pharmaceuticals, Inc.
Cambridge, MA 02142
By: AstraZeneca AB, SE-151 85 Södertälje, Sweden
Product of Sweden

NDC 70785-022-90 **90 Tablets**

 **DUZALLO™**
lesinurad/allopurinol
tablets

200 mg / 300 mg

Dispense the accompanying
Medication Guide to each patient.

Rx only

Ironwood®

Usual Adult Dosage: See full prescribing information.
Store at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]
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GTIN 00370785022901 00-00000

AREA RESERVED
FOR VARIABLE DATA

DUZALLO

lesinurad and allopurinol tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:70785-021
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
lesinurad (UNII: 09ERP08I3W) (lesinurad - UNII:09ERP08I3W)	lesinurad	200 mg
allopurinol (UNII: 63CZ7GJN5I) (allopurinol - UNII:63CZ7GJN5I)	allopurinol	200 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
CROSPVIDONE, UNSPECIFIED (UNII: 2S7830E561)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	

Product Characteristics

Color	ORANGE	Score	no score
Shape	OVAL	Size	17mm
Flavor		Imprint Code	LES200;ALO200
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70785-021-05	5 in 1 BOTTLE; Type 0: Not a Combination Product	10/03/2017	
2	NDC:70785-021-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	10/03/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA209203	10/03/2017	

DUZALLO

lesinurad and allopurinol tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:70785-022
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
lesinurad (UNII: 09ERP08I3W) (lesinurad - UNII:09ERP08I3W)	lesinurad	200 mg
allopurinol (UNII: 63CZ7GJN5I) (allopurinol - UNII:63CZ7GJN5I)	allopurinol	300 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
CROSPVIDONE, UNSPECIFIED (UNII: 2S7830E561)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

FERRIC OXIDE YELLOW (UNII: EX438O2MRT)

TITANIUM DIOXIDE (UNII: 15FIX9V2JP)

TRIACETIN (UNII: XHX3C3X673)

Product Characteristics

Color	BROWN (beige)	Score	no score
Shape	OVAL	Size	19mm
Flavor		Imprint Code	LES200;ALO300
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70785-022-05	5 in 1 BOTTLE; Type 0: Not a Combination Product	10/03/2017	
2	NDC:70785-022-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	10/03/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA209203	10/03/2017	

Labeler - Ironwood Pharmaceuticals, Inc. (054451401)

Revised: 11/2017

Ironwood Pharmaceuticals, Inc.