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Lesinurad and Allopurinol

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Pronunciation

(le SIN ure ad & al oh PURE i nole)

Index Terms

- Allopurinol and Lesinurad

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, Oral:

Duzallo: Lesinurad 200 mg and allopurinol 200 mg [DSC], Lesinurad 200 mg and allopurinol 300 mg [DSC]

Brand Names: U.S.

- Duzallo [DSC]

Pharmacologic Category

- Antigout Agent
- Uric Acid Transporter 1 (URAT1) Inhibitor
- Xanthine Oxidase Inhibitor

Pharmacology

Lesinurad/allopurinol: Lowers serum uric acid levels by increasing excretion and inhibiting production of uric acid.

Allopurinol: Allopurinol inhibits xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine to uric acid. Allopurinol is metabolized to oxypurinol which is also an inhibitor of xanthine oxidase; allopurinol acts on purine catabolism, reducing the production of uric acid without disrupting the biosynthesis of vital purines.

Lesinurad: Lesinurad inhibits the function of transporter proteins involved in renal uric acid reabsorption (uric acid transporter 1 [URAT1] and organic anion transporter 4 [OAT4]), and lowers serum uric acid levels and increases renal clearance and fractional excretion of uric acid in patients with gout.

Absorption

Allopurinol: ~90% from GI tract; lesinurad: rapid

Distribution

Lesinurad: V_{dss}: IV: ~20 L

Metabolism

Allopurinol: Rapidly oxidized, primarily to oxypurinol

Lesinurad: Metabolized oxidatively primarily via CYP2C9; plasma exposure to metabolites is minimal; metabolites are not known to contribute to activity

Excretion

Allopurinol: feces (~20%); lesinurad: urine (63%; ~30% as unchanged drug); feces (32%)

Time to Peak

Allopurinol: 1.5 hours; Oxypurinol: 4.5 hours

Half-Life Elimination

Allopurinol: ~1 to 2 hours; Oxypurinol: ~26 hours; lesinurad: ~5 hours

Protein Binding

Lesinurad: >98%, primarily to albumin

Special Populations: Renal Function Impairment

Lesinurad: Lesinurad exposure increased by 30% in patients with estimated CrCl 60 to <90 mL/minute, 50% to 73% in patients with estimated CrCl 30 to <60 mL/minute, and 113% in patients with estimated CrCl <30 mL/minute, when compared with patients with normal renal function following administration of a single dose.

Special Populations: Hepatic Function Impairment

Lesinurad: AUC was 7% and 33% higher in patients with mild (Child-Pugh class A) and moderate (Child-Pugh class B) impairment following administration of a single dose.

Use: Labeled Indications

Hyperuricemia associated with gout: 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.

Limitations of use: Not recommended for the treatment of asymptomatic hyperuricemia.

Contraindications

Hypersensitivity to allopurinol, including previous occurrence of skin rash, or any component of the formulation; severe renal impairment (CrCl <30 mL/minute), ESRD, kidney transplant recipients, dialysis; tumor lysis syndrome; Lesch-Nyhan syndrome

Note: While not an absolute contraindication, the American College of Rheumatology suggests avoiding the use of allopurinol in patients with the HLA-B*5801 genotype due to the increased risk of allopurinol hypersensitivity syndrome (AHS). The guidelines suggest HLA-B*5801 screening in patients with a high incidence of this genotype; this includes patients of Korean

descent who have stage 3 or worse chronic kidney disease, as well as patients of Han Chinese or Thai descent regardless of kidney function (ACR guidelines [Khanna 2012]).

Dosing: Adult

Note: Use of this combination product is not recommended in patients taking allopurinol <300 mg/day (or <200 mg/day in patients with estimated CrCl <60 mL/min). Gout flare prophylaxis is recommended in patients not currently receiving lesinurad. In clinical trials, colchicine or NSAIDs were given for gout flare prophylaxis during the first 5 months following lesinurad/allopurinol treatment initiation in patients not adequately controlled on allopurinol alone.

Hyperuricemia associated with gout: Oral: 1 tablet (lesinurad 200 mg/allopurinol 200 mg **or** lesinurad 200 mg/allopurinol 300 mg) once daily; maximum dose: Lesinurad 200 mg once daily; do not exceed one tablet per day.

Patients who have not achieved target serum uric acid on a medically appropriate dose of allopurinol >300 mg: Initiate therapy by using one tablet of lesinurad/allopurinol once daily in place of an equivalent portion of the total daily allopurinol dose. Duzallo dosage forms allow for either allopurinol 200 mg or 300 mg once daily.

Patients who have not achieved target serum uric acid on a medically appropriate dose of allopurinol 300 mg: Initiate therapy by using one tablet of lesinurad 200 mg/allopurinol 300 mg once daily in place of allopurinol 300 mg.

Patients who have not achieved target serum uric acid on a medically appropriate dose of allopurinol 200 mg: Initiate therapy by using one tablet of lesinurad 200 mg/allopurinol 200 mg once daily in place of allopurinol 200 mg.

Patients currently on lesinurad in combination with allopurinol: Initiate therapy by using one tablet of lesinurad/allopurinol once daily in place of lesinurad and an equivalent portion of the daily allopurinol dose. Duzallo dosage forms allow for lesinurad 200 mg with either allopurinol 200 mg or 300 mg once daily.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Adjustment for Toxicity

Symptoms indicative of acute uric acid nephropathy (eg, flank pain, nausea, vomiting): Interrupt therapy and measure serum creatinine promptly; do not resume therapy if another cause of serum creatinine abnormalities is not identified.

Administration

Administer in the morning with food and water. Stay well hydrated (eg, 2 liters of liquid per day).

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Drug Interactions

Alpelisib: May decrease the serum concentration of CYP2C9 Substrates (High risk with Inducers). *Monitor therapy*

Aluminum Hydroxide: May decrease the serum concentration of Allopurinol. Management: Consider administering allopurinol 3 hours prior to aluminum hydroxide. *Consider therapy modification*

Amoxicillin: Allopurinol may enhance the potential for allergic or hypersensitivity reactions to Amoxicillin. *Monitor therapy*

Ampicillin: Allopurinol may enhance the potential for allergic or hypersensitivity reactions to Ampicillin. *Monitor therapy*

Angiotensin-Converting Enzyme Inhibitors: May enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Consider therapy modification*

Aspirin: May diminish the therapeutic effect of Lesinurad. *Monitor therapy*

AzaTHIOprine: Allopurinol may increase serum concentrations of the active metabolite(s) of AzaTHIOprine. More specifically, allopurinol may increase mercaptopurine serum concentrations and promote formation of active thioguanine nucleotides. Management: Reduce the azathioprine dose to one third to one quarter of the usual dose if used concomitantly with allopurinol, and monitor closely for systemic toxicity (particularly hematologic toxicity, nausea, and vomiting). *Consider therapy modification*

Bacampicillin: Allopurinol may enhance the potential for allergic or hypersensitivity reactions to Bacampicillin. *Monitor therapy*

Bendamustine: Allopurinol may enhance the adverse/toxic effect of Bendamustine. Specifically, the risk of severe skin reactions may be enhanced. *Monitor therapy*

Capecitabine: Allopurinol may decrease serum concentrations of the active metabolite(s) of Capecitabine. *Avoid combination*

CarBAMazepine: Allopurinol may increase the serum concentration of CarBAMazepine. *Monitor therapy*

CloZAPine: CYP3A4 Inducers (Weak) may decrease the serum concentration of CloZAPine. *Monitor therapy*

Cyclophosphamide: Allopurinol may enhance the adverse/toxic effect of Cyclophosphamide. Specifically, bone marrow suppression. *Monitor therapy*

CycloSPORINE (Systemic): Allopurinol may increase the serum concentration of CycloSPORINE (Systemic). *Monitor therapy*

CYP2C9 Inducers (Moderate): May decrease the serum concentration of Lesinurad. *Monitor therapy*

CYP2C9 Inhibitors (Moderate): May increase the serum concentration of Lesinurad. *Monitor therapy*

Dabrafenib: May decrease the serum concentration of CYP2C9 Substrates (High risk with Inducers). Management: Seek alternatives to the CYP2C9 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Consider therapy modification*

Didanosine: Allopurinol may increase the serum concentration of Didanosine. *Avoid combination*

Doxofylline: Allopurinol may increase the serum concentration of Doxofylline. *Monitor therapy*

Enzalutamide: May decrease the serum concentration of CYP2C9 Substrates (High risk with Inducers). Management: Concurrent use of enzalutamide with CYP2C9 substrates that have a narrow therapeutic index should be avoided. Use of enzalutamide and any other CYP2C9 substrate should be performed with caution and close monitoring. *Consider therapy modification*

Estrogen Derivatives (Contraceptive): Lesinurad may decrease the serum concentration of Estrogen Derivatives (Contraceptive). Management: Use of an additional, nonhormonal contraceptive is recommended in patients being treated with lesinurad who desire effective contraception. *Consider therapy modification*

Loop Diuretics: May enhance the adverse/toxic effect of Allopurinol. Loop Diuretics may increase the serum concentration of Allopurinol. Specifically, Loop Diuretics may increase the concentration of Oxypurinol, an active metabolite of Allopurinol. *Monitor therapy*

Lumacaftor and Ivacaftor: May decrease the serum concentration of CYP2C9 Substrates (High Risk with Inhibitors or Inducers). Lumacaftor and Ivacaftor may increase the serum concentration of CYP2C9 Substrates (High Risk with Inhibitors or Inducers). *Monitor therapy*

Mercaptopurine: Allopurinol may increase the serum concentration of Mercaptopurine. Allopurinol may also promote formation of active thioguanine nucleotides. Management: Reduce the mercaptopurine dose to one third to one quarter of the usual dose if used with allopurinol, and monitor closely for systemic toxicity. US labeling for mercaptopurine oral suspension (Purixan brand) recommends avoiding allopurinol. *Consider therapy modification*

MiFEPRIStone: May increase the serum concentration of CYP2C9 Substrates (High risk with Inhibitors). Management: Use CYP2C9 substrates at the lowest recommended dose, and monitor closely for adverse effects, during and in the 2 weeks following mifepristone treatment. *Consider therapy modification*

NiMODipine: CYP3A4 Inducers (Weak) may decrease the serum concentration of NiMODipine. *Monitor therapy*

Pegloticase: Allopurinol may enhance the adverse/toxic effect of Pegloticase. Specifically, Allopurinol may blunt increases in serum urate that would signal an increased risk of anaphylaxis and infusion reactions. *Avoid combination*

Progestins (Contraceptive): Lesinurad may decrease the serum concentration of Progestins (Contraceptive). Management: Use of an additional, nonhormonal contraceptive is recommended in patients being treated with lesinurad who desire effective contraception. *Consider therapy modification*

Rifapentine: May decrease the serum concentration of CYP2C9 Substrates (High risk with Inducers). *Monitor therapy*

Riluzole: Allopurinol may enhance the adverse/toxic effect of Riluzole. Specifically, the risk of hepatotoxicity may be increased. Management: Consider alternatives to allopurinol in patients receiving treatment with riluzole due to the potential for additive hepatotoxicity. *Consider therapy modification*

Tacrolimus (Systemic): CYP3A4 Inducers (Weak) may decrease the serum concentration of Tacrolimus (Systemic). *Monitor therapy*

Tegafur: Allopurinol may diminish the therapeutic effect of Tegafur. *Avoid combination*

Theophylline Derivatives: Allopurinol may increase the serum concentration of Theophylline Derivatives. **Exceptions:** Dyphylline. *Monitor therapy*

Thiazide and Thiazide-Like Diuretics: May enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide and Thiazide-Like Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinol, an active metabolite of Allopurinol. *Monitor therapy*

Ubrogepant: CYP3A4 Inducers (Weak) may decrease the serum concentration of Ubrogepant. Management: Use an initial ubrogepant dose of 100 mg and second dose (if needed) of 100 mg when used with a weak CYP3A4 inducer. *Consider therapy modification*

Valproate Products: May increase the serum concentration of Lesinurad. *Avoid combination*

Vitamin K Antagonists (eg, warfarin): Allopurinol may enhance the anticoagulant effect of Vitamin K Antagonists. *Consider therapy modification*

Adverse Reactions

See individual agents.

ALERT: U.S. Boxed Warning

Risk of acute renal failure:
Acute renal failure has occurred with lesinurad, one of the components of Duzallo.

Warnings/Precautions

Concerns related to adverse effects:

• Bone marrow suppression: Bone marrow suppression has been reported in patients receiving allopurinol, most of whom received concomitant medications with a potential for hematologic toxicity. The onset occurs between 6 weeks to 6 years after allopurinol initiation.

• Cardiovascular events: Major cardiac adverse events (cardiovascular deaths, non-fatal MI, or non-fatal strokes) were observed in clinical trials, although a causal relationship was not established.

• CNS effects: May occasionally cause drowsiness; patients must be cautioned about performing tasks that require mental alertness (eg, operating machinery or driving).

• Gout flare: Following initiation of urate-lowering therapy, including lesinurad/allopurinol, gout may flare due to mobilization of urate from tissue deposits; gout flare prophylaxis (such as colchicine or an NSAID) is recommended when initiating treatment in patients not currently taking lesinurad. Lesinurad/allopurinol treatment may continue during gout flare and management of the flare.

• Hepatotoxicity: Cases of hepatotoxicity (reversible) have been reported with allopurinol. Asymptomatic elevations of serum alkaline phosphatase or serum transaminases have been observed. Monitor for signs/symptoms of hepatotoxicity; evaluate liver function if they occur. Periodic liver function tests are recommended in patients with preexisting hepatic impairment.

• Hypersensitivity: Allopurinol has been frequently associated with a skin rash. In some instances a skin rash may be followed by more severe hypersensitivity reactions, including exfoliation, fever, lymphadenopathy, arthralgia, eosinophilia, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Associated vasculitis and tissue response may be manifested as hepatitis, renal impairment, seizures, or death (rare). Use with caution in patients with renal impairment and taking concomitant thiazide diuretics; hypersensitivity reactions may be increased. Discontinue therapy at first sign of skin rash or other signs indicative of allergic reaction. Consider HLA-B*5801 allele testing in patients at a higher risk for allopurinol hypersensitivity syndrome (eg, Korean patients with stage 3 or worse CKD and Han Chinese and Thai descent regardless of renal function) prior to initiation of therapy (ACR guidelines [Khanna 2012]).

• Nephrotoxicity: Lesinurad, when used concurrently with a xanthine oxidase inhibitor, is associated with an increased incidence of serum creatinine elevations (generally reversible). **[US Boxed Warning]: Acute renal failure has occurred with lesinurad** and was more common when lesinurad was given alone. Renal failure (acute and chronic) and nephrolithiasis have also been reported (when used in combination with a xanthine oxidase inhibitor). The incidence of renal-related adverse events was also higher with lesinurad dosed at 400 mg (which is higher than the approved dose). If serum creatinine increases >2 times the baseline, interrupt treatment. If symptoms of acute uric acid nephropathy (eg, flank pain, nausea, vomiting) are reported, interrupt treatment and measure creatinine promptly; do not restart therapy without another explanation for serum creatinine abnormalities.

Disease-related concerns:

• Renal impairment: Evaluate renal function prior to treatment initiation and periodically thereafter. Evaluate more frequently in patients with estimated CrCl <60 mL/minute or with serum creatinine elevations 1.5 to 2 times the baseline level. Do not initiate in patients with estimated CrCl <45 mL/minute; discontinue therapy if estimated CrCl <45 mL/minute persistently (contraindicated with CrCl <30 mL/minute).

• Secondary hyperuricemia: Lesinurad has not been studied in patients with secondary hyperuricemia (including organ transplant recipients); use is contraindicated in patients with tumor lysis syndrome or Lesch-Nyhan syndrome, where the uric acid formation rate is greatly increased.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant drug interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Special populations:

• CYP2C9 poor metabolizers: Lesinurad exposure is ~1.8 fold higher in CYP2C9 poor metabolizers; use with caution in CYP2C9 poor metabolizers and patients taking concomitant moderate CYP2C9 inhibitors.

Monitoring Parameters

CBC, serum uric acid levels every 2 to 5 weeks during dose titration until desired level is achieved and every 6 months thereafter (ACR guidelines [Khanna 2012]), liver function tests (periodically in patients with preexisting hepatic disease), renal function (BUN, serum creatinine or creatinine clearance [prior to initiation and periodically]; more frequently in patients with estimated CrCl <60 mL/minute or with serum creatinine elevations 1.5 to 2 times the baseline level), prothrombin time (periodically in patients receiving warfarin); consider HLA-B*5801 testing prior to initiation of therapy in patients at a higher risk for allopurinol hypersensitivity syndrome (see Contraindications) (ACR guidelines [Khanna 2012]). Monitor hydration status, for signs and symptoms of hypersensitivity, hepatotoxicity.

Pregnancy Considerations

Animal reproduction studies have not been conducted with this combination. See individual monographs for additional information.

All forms of hormonal contraceptives (eg, oral, injectable, topical) may be less effective during therapy with lesinurad. Additional methods of contraception are recommended during therapy.

Patient Education

• Discuss specific use of drug and side effects with patient as it relates to treatment. (HCAHPS: During this hospital stay, were you given any medicine that you had not taken before? Before giving you any new medicine, how often did hospital staff tell you what the medicine was for? How often did hospital staff describe possible side effects in a way you could understand?)

• Patient may experience headache, flu-like signs, heartburn, diarrhea, or fatigue. Have patient report immediately to prescriber signs of infection, signs of liver problems (dark urine, fatigue, lack of appetite, nausea, abdominal pain, light-colored stools, vomiting, or yellow skin), signs of kidney problems (unable to pass urine, blood in the urine, change in amount of urine passed, or weight gain), nausea, vomiting, lower back pain, side pain, painful urination, swollen glands, joint pain, seizures, or signs of Stevens-Johnson syndrome/toxic epidermal necrolysis (red, swollen, blistered, or peeling skin [with or without fever]; red or irritated eyes; or sores in mouth, throat, nose, or eyes) (HCAHPS).

• Educate patient about signs of a significant reaction (eg, wheezing; chest tightness; fever; itching; bad cough; blue skin color; seizures; or swelling of face, lips, tongue, or throat). **Note:** This is not a comprehensive list of all side effects. Patient should consult prescriber for additional questions.

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