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Lesinurad

Class: Uricosuric Agents
Chemical Name: 2-[[5-bromo-4-(4-cyclopropyl-1-naphthalenyl)-4H-1,2,4-triazol-3-yl]thio]-acetic acid
Molecular Formula: $C_{17}H_{14}BrN_3O_2S$
CAS Number: 878672-00-5
Brands: Zurampic

Medically reviewed by Drugs.com. Last updated on Mar 12, 2020.

Warning

- Acute renal failure reported; more common when lesinurad administered as monotherapy.[1] Use lesinurad in combination with a xanthine oxidase inhibitor (e.g., allopurinol, febuxostat).[1] (See Renal Effects under Cautions.)

Introduction

Uricosuric agent; uric acid transporter 1 (URAT1) and organic anion transporter 4 (OAT4) inhibitor.[1 2 4 5 6 8]

Uses for Lesinurad

Hyperuricemia Associated with Gout

Management of hyperuricemia associated with gout in patients who have not attained target serum uric acid concentrations with xanthine oxidase inhibitor monotherapy; use in combination with a xanthine oxidase inhibitor (e.g., allopurinol, febuxostat).[1 10]

American College of Rheumatology states that serum urate concentrations in gout patients should be reduced sufficiently to result in durable improvement in signs and symptoms of the disease and recommends a target serum urate concentration of <6 mg/dL (or <5 mg/dL if necessary to achieve such clinical improvements).[11]

Do not use as monotherapy.[1] (See Renal Effects under Cautions.)

Not recommended in patients with normal renal function who are receiving allopurinol dosages <300 mg daily or in patients with estimated Cl_{cr} <60 mL/minute who are receiving allopurinol dosages <200 mg daily.[1]

Not expected to be effective in patients with severe renal impairment; use is contraindicated in such patients.[1] (See Renal Impairment under Cautions.)

Not recommended for management of asymptomatic hyperuricemia.[1]

Safety and efficacy not established in patients with secondary hyperuricemia (including that occurring in organ transplant recipients).[1]

Contraindicated in patients with tumor lysis syndrome or Lesch-Nyhan syndrome, conditions associated with greatly increased rates of uric acid formation.[1]

Lesinurad Dosage and Administration

General

- Assess renal function before initiating lesinurad and periodically thereafter as clinically appropriate.[1] Do not initiate in patients with estimated Cl_{cr} <45 mL/minute.[1]
- Because initiation of urate-lowering therapy is associated with an increased frequency of acute gouty attacks (gout flare), gout flare prophylaxis is recommended upon initiation of lesinurad according to standard of care.[1] If a gout flare occurs during therapy, continue lesinurad and manage the gout flare as appropriate for the patient.[1]
- Patients should remain well hydrated (e.g., by drinking 2 L of fluids daily) during therapy.[1]

Administration

Oral Administration

Administer orally in the morning with food and water at the same time as the morning dose of the xanthine oxidase inhibitor.[1]

Interrupt lesinurad if xanthine oxidase inhibitor is interrupted.[1] Failure to take lesinurad with a xanthine oxidase inhibitor may result in increased risk of adverse renal effects.[1] (See Renal Effects under Cautions.)

Dosage

Adults

Hyperuricemia Associated with Gout

Oral

200 mg once daily.[1] Use in combination with a xanthine oxidase inhibitor (e.g., allopurinol, febuxostat).[1]

Interrupt lesinurad if S_{cr} >2 times the baseline value.[1] Interrupt lesinurad and promptly measure S_{cr} if symptoms suggestive of acute uric acid nephropathy (e.g., flank pain, nausea or vomiting) are present.[1] Rule out lesinurad as the cause of S_{cr} abnormalities prior to reinitiating the drug.[1]

Discontinue lesinurad if estimated Cl_{cr} is persistently <45 mL/minute.[1]

Prescribing Limits

Adults

Hyperuricemia Associated with Gout

Oral

Maximum 200 mg once daily.[1] (See Renal Effects under Cautions.)

Special Populations

Hepatic Impairment

Mild or moderate hepatic impairment (Child-Pugh class A or B): Dosage adjustment not necessary.[1]

Severe hepatic impairment: Not studied; use not recommended.[1]

Renal Impairment

Dosage adjustment not necessary in patients with estimated Cl_{cr} ≥45 mL/minute.[1] Use not recommended in patients with estimated Cl_{cr} <45 mL/minute.[1]

Geriatric Patients

Dosage adjustment not necessary based solely on age.[1 9] However, consider potential for age-related decreased renal function.[9]

Cautions for Lesinurad

Contraindications

- Patients with severe renal impairment (estimated Cl_{cr} <30 mL/minute) or end-stage renal disease, patients undergoing dialysis, renal transplant recipients, and patients with tumor lysis syndrome or Lesch-Nyhan syndrome.[1]

Warnings/Precautions

Warnings

Risk of Acute Renal Failure

Acute renal failure reported; more common when lesinurad administered as monotherapy.[1] Use in combination with a xanthine oxidase inhibitor (e.g., allopurinol, febuxostat).[1] (See Renal Effects under Cautions.)

Other Warnings/Precautions

Renal Effects

Lesinurad increases renal excretion of uric acid, which can result in uric acid microcrystallization in the renal tubule or urinary system, potentially resulting in acute uric acid nephropathy or renal stones.[1 5 10] Combined use with a xanthine oxidase inhibitor, which blocks uric acid production, reduces the amount of uric acid available for excretion and decreases the risk of adverse renal effects.[4 9]

Therapy with lesinurad 200 mg daily (maximum recommended dosage) in combination with a xanthine oxidase inhibitor associated with increased S_{cr} (generally reversible), adverse renal-related effects, and renal stones.[1] Higher incidence of increased S_{cr} and adverse renal-related effects, including acute renal failure, reported with lesinurad 400 mg daily; highest incidence occurred with the 400-mg dosage given as monotherapy.[1]

Adverse renal effects reported in patients with normal or impaired renal function, but incidence is higher in patients with moderate renal impairment compared with those with mild renal impairment or normal baseline renal function.[1]

Do not use lesinurad as monotherapy; do not initiate in patients with estimated Cl_{cr} <45 mL/minute.[1]

Evaluate renal function prior to initiating therapy and periodically thereafter as clinically indicated.[1] More frequent monitoring recommended in patients with estimated Cl_{cr} <60 mL/minute or with S_{cr} elevations of 1.5–2 times the baseline value.[1]

Treatment interruption or discontinuance may be necessary in patients with adverse renal effects.[1] (See Dosage under Dosage and Administration.)

Cardiovascular Events

Major adverse cardiovascular events (i.e., cardiovascular death, nonfatal MI, nonfatal stroke) reported in clinical studies; causal relationship not established.[1]

Specific Populations

Pregnancy

Data not available regarding use in pregnant women.[1] Animal studies revealed no evidence of teratogenicity, embryofetal toxicity, or adverse developmental effects.[1]

Lactation

Not known whether lesinurad is distributed into human milk or has any effects on breast-fed infants or on milk production.[1] Distributed into milk in rats in concentrations approximately equivalent to plasma concentrations.[1]

Consider the benefits of breast-feeding along with the importance of the drug to the woman and any potential adverse effects on the breast-fed infant from the drug or from the underlying maternal condition.[1]

Pediatric Use

Safety and efficacy in pediatric patients <18 years of age not established.[1]

Geriatric Use

No overall differences in safety and efficacy observed between geriatric patients and younger adults.[1] However, possibility of greater sensitivity of some older patients cannot be ruled out.[1]

Hepatic Impairment

Mild or moderate hepatic impairment does not substantially alter lesinurad pharmacokinetics.[1,4]

Not studied in patients with severe hepatic impairment and not recommended in this population.[1]

Renal Impairment

AUC is increased in patients with renal impairment.[1] (See Special Populations under Pharmacokinetics: Absorption.)

In clinical studies of combination lesinurad and xanthine oxidase inhibitor therapy, 62% of patients had mild or moderate renal impairment.[1] No clear differences in safety and efficacy in patients with mild renal impairment (estimated Cl_{cr} 60 to <90 mL/minute) compared with those with normal renal function.[1] Patients with moderate renal impairment (estimated Cl_{cr} 30 to <60 mL/minute) had higher incidence of adverse renal effects compared with those with mild renal impairment or normal renal function.[1] (See Renal Effects under Cautions.) Trend toward lesser

efficacy observed in patients with estimated Cl_{cr} <45 mL/minute (only limited experience in this population).[1]

Efficacy and safety not established in those with severe renal impairment (estimated Cl_{cr} <30 mL/minute) or end-stage renal disease, or in those undergoing dialysis; not expected to be effective in these patients.[1] Contraindicated in these patients and in renal transplant recipients.[1]

Assess renal function before initiating lesinurad and periodically thereafter as clinically appropriate; more frequent monitoring recommended in patients with estimated Cl_{cr} <60 mL/minute or with increases in S_{cr} to 1.5–2 times the baseline value.[1] Do not initiate in patients with estimated Cl_{cr} <45 mL/minute; discontinue lesinurad if estimated Cl_{cr} is persistently <45 mL/minute.[1]

Poor CYP2C9 Metabolizers

Use with caution in patients who are poor CYP2C9 metabolizers; lesinurad exposure may be increased.[1] (See Special Populations under Pharmacokinetics: Absorption.)

Common Adverse Effects

Headache,[1 10] influenza,[1] increased S_{cr},[1 10] GERD.[1]

Interactions for Lesinurad

Metabolized principally by CYP2C9.[1] Weak inducer of CYP3A; causes no clinically important induction of CYP1A2, 2B6, 2C8, 2C9, or 2C19 and no clinically important inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4.[1]

Substrate for OAT1 and OAT3 in vitro, but no clinical interaction studies to date with OAT1 and OAT3 inhibitors.[1]

Inhibitor of organic anion transporter protein (OATP) 1B1, OAT1 and OAT3, and organic cation transporter 1 (OCT1) in vitro but not in vivo.[1] No clinically important effect on P-glycoprotein in vitro.[1]

Drugs Affecting or Affected by Hepatic Microsomal Enzymes

CYP2C9 inhibitors: Increased lesinurad exposure.[1] Use lesinurad and moderate CYP2C9 inhibitors concomitantly with caution.[1]

Moderate CYP2C9 inducers: Decreased exposure and possible reduced efficacy of lesinurad.[1]

CYP3A substrates: Possible decreased plasma concentrations of sensitive CYP3A substrates.[1 9] Consider possible reduced efficacy of CYP3A substrate drugs and monitor for efficacy.[1 9]

Specific Drugs

Drug	Interaction	Comments
Amiodarone	Possible increased lesinurad exposure[1]	Use concomitantly with caution[1]
Amlodipine	Amlodipine AUC and peak plasma concentration decreased by about 40%[1 7]	Monitor for possible reduced efficacy of amlodipine[1]

Antacids (aluminum and magnesium hydroxides, calcium carbonate)	No substantial effect on AUC or peak plasma concentration of lesinurad[1]	No dosage adjustment necessary[1]
Aspirin	Aspirin may alter URAT1 inhibitory effects of lesinurad[7] Aspirin (>325 mg daily): Possible reduced lesinurad efficacy[1] Aspirin (≤325 mg daily): No evidence in clinical trials of reduced lesinurad efficacy[1 9]	Lesinurad and aspirin at dosages ≤325 mg daily (i.e., for cardiovascular protection) may be used concomitantly[1 9]
Carbamazepine	Possible decreased exposure and decreased efficacy of lesinurad[1]	
Colchicine	No substantial effect on colchicine pharmacokinetics[1 7]	No dosage adjustment necessary[1]
Epoxide hydrolase inhibitors (e.g., valproic acid)	Possible interference with lesinurad metabolism[1]	Avoid concomitant use[1]
Fluconazole	Lesinurad AUC and peak plasma concentration increased by 56 and 38%, respectively[1 7]	Use concomitantly with caution[1]
Furosemide	Furosemide AUC and peak plasma concentration decreased by 31 and 51%, respectively, but no change in diuretic activity[1 7]	No dosage adjustment necessary[1]
HMG-CoA reductase inhibitors (statins) (e.g., atorvastatin)	No substantial change in atorvastatin exposure; possible decreased exposure to statins that are more sensitive CYP3A substrates [1 7 9]	Atorvastatin: No dosage adjustment necessary[1] Consider potential for reduced efficacy of statins that are sensitive CYP3A substrates and monitor for efficacy[1]
Hormonal contraceptives (oral, injectable, transdermal, implants)	Possible decreased plasma concentrations and decreased efficacy of the contraceptive[1 9]	Do not rely solely on hormonal contraceptives; use additional methods of contraception[1]
Metformin	No change in metformin AUC or peak plasma concentration[1]	No dosage adjustment necessary[1]
NSAIAs (indomethacin, naproxen)	Indomethacin, naproxen: No substantial effect on pharmacokinetics of lesinurad or the NSAIA[1 7]	No dosage adjustment necessary[1]

Ranitidine	No substantial effect on lesinurad pharmacokinetics[1]	No dosage adjustment necessary[1]
Repaglinide	No substantial effect on AUC or peak plasma concentration of repaglinide[1]	No dosage adjustment necessary[1]
Rifampin	Lesinurad AUC and peak plasma concentration decreased by 38 and 24%, respectively[1 7 9]	Monitor for possible reduced efficacy of lesinurad[1]
Sildenafil	Sildenafil AUC and peak plasma concentration decreased by about 34%[1 7]	Monitor for possible reduced efficacy of sildenafil[1]
Tolbutamide	No substantial effect on AUC or peak plasma concentration of tolbutamide[1]	No dosage adjustment necessary[1]
Warfarin	No substantial effect on warfarin pharmacokinetics (AUC, peak plasma concentration) or pharmacodynamics (INR)[1 7]	No dosage adjustment necessary[1]
Xanthine oxidase inhibitors (allopurinol, febuxostat)	Allopurinol, febuxostat: No substantial effect on pharmacokinetics of lesinurad or the xanthine oxidase inhibitor[7]	Differing mechanisms of action used to therapeutic advantage in lowering elevated serum uric acid concentrations in patients with gout[1 7 9]

Lesinurad Pharmacokinetics

Absorption

Bioavailability

Rapidly and completely absorbed following oral administration.[1 7]

Peak plasma concentration attained within 1–4 hours under fasted or fed conditions.[1]

Peak plasma concentration and AUC increase in a dose-dependent manner.[1]

Food

Administration with a high-fat meal reduces peak plasma concentration by up to 18% but does not alter AUC.[1]

Special Populations

Mild or moderate (Child-Pugh class A or B) hepatic impairment: AUC increased by 7 or 33%, respectively, compared with individuals with normal hepatic function.[1]

Mild, moderate, or severe renal impairment: AUC increased by 30, 50–73, or 113%, respectively, compared with individuals with normal renal function.[1]

Poor CYP2C9 metabolizers: Exposure increased by approximately 1.8-fold compared with extensive metabolizers.[1]

Distribution

Extent

Not known whether distributed into human milk.[1]

Plasma Protein Binding

>98%, principally to albumin.[1]

Special Populations

Renal or hepatic impairment does not substantially alter plasma protein binding of lesinurad.[1]

Elimination

Metabolism

Principally via CYP2C9.[1]

Elimination Route

63 and 32% of radiolabeled dose recovered in urine and feces, respectively.[1] Unchanged lesinurad in urine accounted for approximately 30% of administered dose.[1]

Half-life

Approximately 5 hours.[1]

Stability

Storage

Oral

Tablets

20–25°C (may be exposed to 15–30°C).[1] Protect from light.[1]

Actions

- Reduces serum uric acid concentrations via inhibition of URAT1 and OAT4, 2 apical transporter proteins in the OAT family[6] involved in renal reabsorption of uric acid.[1 8] URAT1 accounts for majority of reabsorption of filtered uric acid from renal tubular lumen;[1] OAT4 is associated with diuretic-induced hyperuricemia.[1 8]
- Does not inhibit glucose transporter 9 (GLUT9), a uric acid reabsorption transporter located on the basolateral membrane of the proximal tubule cell.[1 5 8]
- More selective than probenecid, which inhibits URAT1, OAT4, and other OAT family members (OAT1 and OAT3) in the clinical setting.[2 8]
- Increases renal clearance and fractional excretion of uric acid and lowers serum uric acid concentrations in a dose-dependent manner in patients with gout.[1] Combined use with a xanthine oxidase inhibitor, which blocks uric acid production, reduces amount of uric acid available for excretion and decreases risk of adverse renal effects.[4 9]

Advice to Patients

- Importance of reading the manufacturer's medication guide before beginning lesinurad therapy and each time the prescription is refilled.[1]
- Importance of using lesinurad concomitantly with a xanthine oxidase inhibitor and of discontinuing lesinurad if the xanthine oxidase inhibitor is discontinued.[1] Advise patients to take lesinurad in the morning with food and water at the same time as the xanthine oxidase inhibitor and to stay well-hydrated (e.g., by drinking 2 L [68 ounces] of fluids daily).[1]
- Importance of informing patients that if a dose of lesinurad is missed, not to take the missed dose later in the day.[1] Advise patients to omit the missed dose and resume the regular dosing schedule the following day; instruct patients to not double the dose.[1]
- Risk of adverse renal effects (e.g., transient increases in S_{cr}, renal stones, acute renal failure); importance of periodic monitoring of S_{cr}.[1]
- Potential for gout flares to occur following initiation of lesinurad therapy; importance of receiving prophylactic therapy for gout flares upon initiation of lesinurad.[1] Advise patients not to discontinue lesinurad if a gout flare occurs during treatment.[1]
- Importance of informing women of childbearing potential not to rely solely on hormonal contraceptives and to use additional methods of contraception when receiving lesinurad.[1]
- Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.[1]
- Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses.[1]
- Importance of informing patients of other important precautionary information.[1] (See Cautions.)

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

*Please refer to the **ASHP Drug Shortages Resource Center** for information on shortages of one or more of these preparations.*

Lesinurad

Routes	Dosage Forms	Strengths	Brand Names	Manufacturer
Oral	Tablets, film-coated	200 mg	Zurampic	AstraZeneca

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