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MONOGRAPH

LESINURAD SODIUM

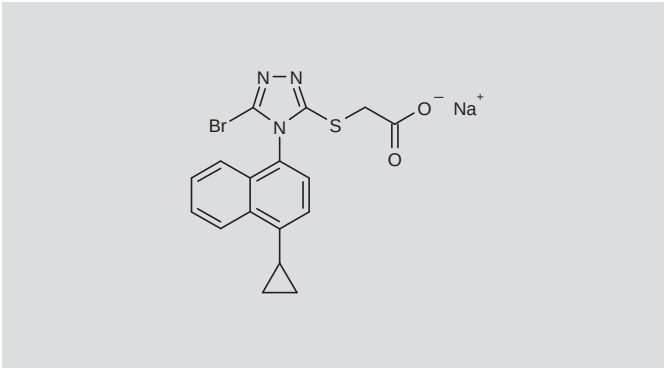
Prop INN; USAN

Solute Carrier Family 22 Member 12 (URAT1) Inhibitor
Uricosuric
Treatment of Gout

RDEA-594

2-[5-Bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylsulfanyl]acetic acid sodium salt

InChI: 1S/C17H14BrN3O2S.Na/c18-16-19-20-17(24-9-15(22)23)21(16)14-8-7-11(10-5-6-10)12-3-1-2-4-13(12)14;/h1-4,7-8,10H,5-6,9H2,(H,22,23);/q;+1/p-1



$C_{17}H_{13}BrN_3NaO_2S$
Mol wt: 426.263
EN: 478314

SUMMARY

Gout is the most common form of inflammatory arthritis in men over 40 years of age. Available drugs target various steps to lower serum urate levels and include the xanthine oxidase inhibitors allopurinol and febuxostat, as well as the uricosuric agents probenecid, sulfinpyrazone and benzbromarone. Current treatment options are limited, associated with adverse events and often have an inadequate response. These factors have driven the need for the development of new and alternative agents to lower uric acid levels. In this context, lesinurad sodium (RDEA-594), an active metabolite of RDEA-806, was noted to have significant uricosuric effects by inhibiting solute carrier family 22 member 12 (urate anion exchanger 1, URAT1). URAT1 is a primary transporter of uric acid. In clinical trials, lesinurad sodium has been well tolerated, with dose-dependent reductions in serum uric acid. Moreover, co-administration of xanthine oxidase inhibitors and lesinurad sodium can safely accelerate urate reduction in gout patients.

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*Synthesis prepared by C. Estivill, R. Castañer. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

SYNTHESIS*

Lesinurad sodium can be prepared by several different ways:

Cyclization of 4-cyclopropyl-1-naphthyl isothiocyanate (I) with aminoguanidine hydrochloride (II) using DIEA in DMF yields the naphthyl-1,2,4-triazole-3-thiol (III), which is then alkylated with methyl chloroacetate (IV) by means of K_2CO_3 in DMF to give the (triazolylsulfanyl)acetate (V). Diazotization of the amine (V) with $NaNO_2$ and $Cl_2CHCOOH$ in the presence of $BnEt_3NBr$ or $BnEt_3NCl$ in $CHBr_3$ gives rise to the 5-bromotriazole derivative (VI), which is hydrolyzed with LiOH in THF/EtOH/H_2O to produce lesinurad (VII) (1-3), and is finally treated with NaOH in EtOH (2, 3). Scheme 1.

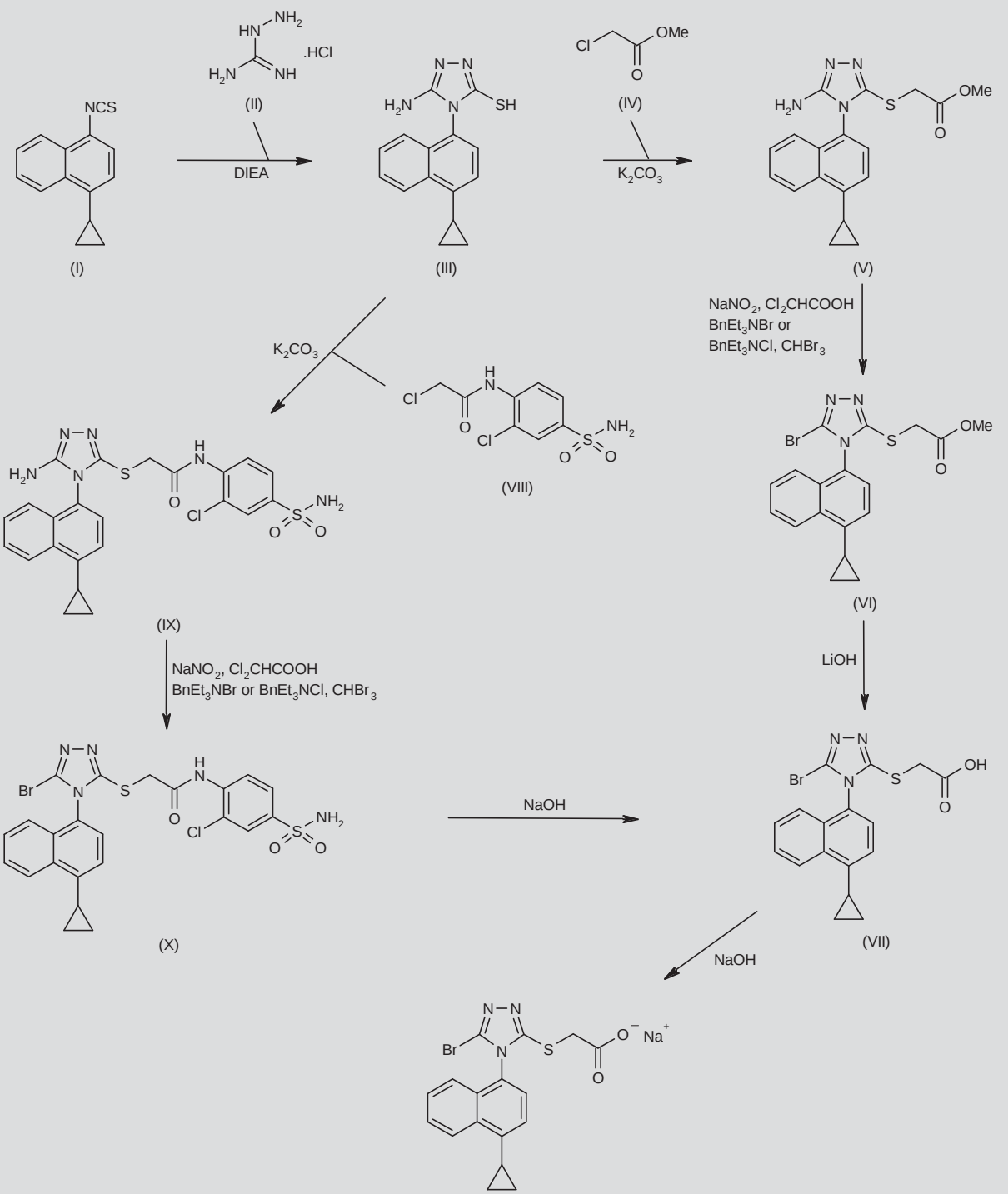
Also, coupling of the thiol (III) with the 2-chloroacetamide derivative (VIII) by means of K_2CO_3 in DMF yields the amide (IX), which is then brominated with $CHBr_3$ in the presence of $NaNO_2$, $Cl_2CHCOOH$ and $BnEt_3NBr$ or $BnEt_3NCl$ to give the 5-bromotriazole derivative (X) (1). Finally, hydrolysis of amide (X) with NaOH in refluxing EtOH affords lesinurad (VII) (2, 3). Scheme 1.

Intermediate 4-cyclopropyl-1-naphthyl isothiocyanate (I) can be prepared by the following strategies:

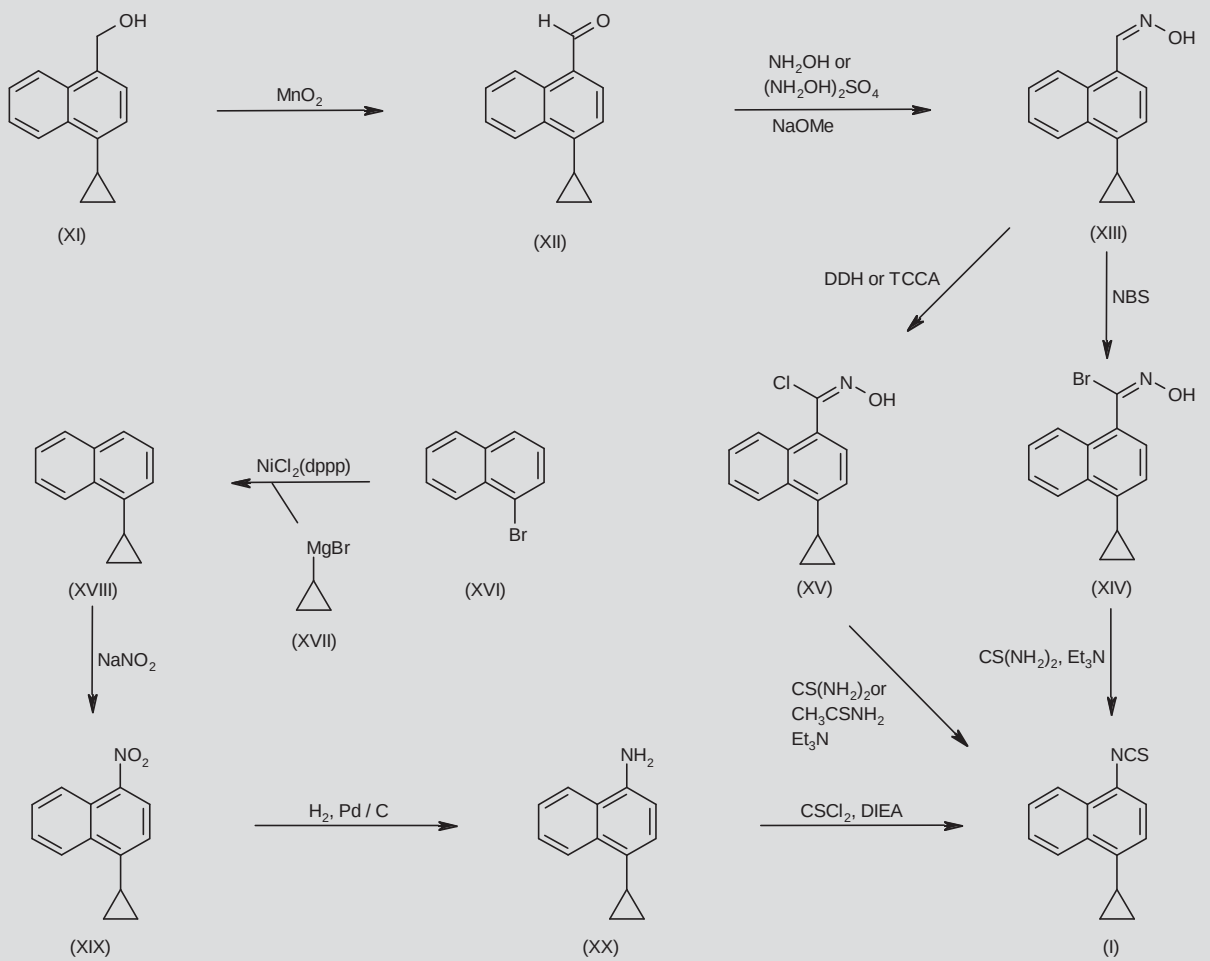
Oxidation of (4-cyclopropyl-1-naphthyl)methanol (XI) by means of MnO_2 in CH_2Cl_2 yields 4-cyclopropyl-1-naphthaldehyde (XII), which is then treated with $NH_2OH{\cdot}HCl$ or $(NH_2OH)_2SO_4$ in the presence of NaOMe (generated from Na in MeOH) to give 4-cyclopropyl-1-naphthaldehyde oxime (XIII). Bromination of oxime (XIII) with NBS in acetonitrile provides the corresponding oximidoyl bromide (XIV), which is finally treated with $CS(NH_2)_2$ in the presence of Et_3N in THF (I) (4). Scheme 2.

Chlorination of oxime (XIII) using 1,3-dichloro-5,5-dimethylhydantoin (DDH) or trichloroisocyanuric acid (TCCA) in acetonitrile affords 4-cyclopropyl-*N*-hydroxynaphthalene-1-carboximidoyl chloride (XV), which is then treated with $CS(NH_2)_2$ or CH_3CSNH_2 in the presence of Et_3N in THF (4). Scheme 2.

Scheme 1. Synthesis of Lesinurad Sodium



Scheme 2. Synthesis of Intermediate (I)



Coupling of 1-bromonaphthalene (XVI) with cyclopropylmagnesium bromide (XVII) in the presence of $NiCl_2$(dppp) in THF gives 1-cyclopropylnaphthalene (XVIII), which is then nitrated with $NaNO_2$ at 0 °C to produce 1-cyclopropyl-4-nitronaphthalene (XIX). Reduction of the nitronaphthalene derivative (XIX) by means of H_2 over Pd/C in EtOH yields 4-cyclopropyl-1-naphthylamine (XX), which is finally treated with $CSCl_2$ and DIEA in CH_2Cl_2 at 0 °C (1-3). Scheme 2.

BACKGROUND

Gout affects approximately 8.3 million Americans, predominantly men (5). Humans are the only mammals who develop gout spontaneously due to mutational loss of the hepatic enzyme uricase (urate oxidase), which oxidizes uric acid to a more soluble compound, allantoin (6).

The most important risk factor for developing gout is hyperuricemia. Serum urate concentration is determined by the balance between production and elimination. Impairment of renal excretion of uric acid is the main cause of hyperuricemia (90%), and it is therefore a clinically significant target for therapy (7, 8). In man, most filtered urate is reabsorbed, followed by its secretion and post-secretory reabsorption into the renal proximal tubule, with only about 10% excretion in the urine (9).

Most patients with gout have inefficient renal excretion of uric acid as the mechanism of hyperuricemia (9, 10). Renal transport of uric acid is governed by a complex system of transporters in the proximal tubule (8, 11). Solute carrier family 22 member 12 (urate anion exchanger 1, URAT1) in human kidney (encoded by *SLC22A12*) was

identified as a primary transporter of uric acid. URAT1 is expressed only in the kidney and is located at the apical (luminal) membrane of proximal tubules. URAT1 constitutes a specific pathway for urate reabsorption in exchange for monocarboxylates from the tubular lumen (extracellular) to the cytosol (intracellular) at the proximal tubules (12, 13).

Various uricosuric substances reduce hyperuricemia, including probenecid, phenylbutazone, sulfinpyrazone, acetylsalicylic acid and losartan. They effectively inhibit URAT1. Benzbromarone is the most potent, completely inhibiting urate uptake via URAT1 (12, 13). Solute carrier family 22 (organic anion transporter 4; *OAT4*) appears to have a similar role in exchanging uric acid for dicarboxylates (14). Glucose transporter type 9 (GLUT-9; *SLC2A9*) inhibits the reabsorption of uric acid into the circulation, along with glucose and fructose (15-18). Probenecid, sulfinpyrazone and benzbromarone are traditional uricosuric drugs used for the treatment of gout. These drugs are now known to inhibit uric acid reabsorption by URAT1 and GLUT-9 (17-19).

Lesinurad sodium is an active metabolite of RDEA-806, a novel nonnucleoside reverse transcriptase inhibitor (NNRTI), an antiviral drug that was first used in clinical trials to treat patients with HIV. It was discovered fortuitously that lesinurad sodium has substantial uricosuric effects.

PRECLINICAL PHARMACOLOGY

The inhibitory effect of lesinurad sodium on serum uric acid (sUA) uptake was demonstrated in in vitro studies using URAT1 expressed in *Xenopus* oocytes (20).

Solute carrier family 22 member 6 (organic anion transporter 1, hOAT1) and solute carrier family 22 member 8 (organic anion transporter 3, hOAT3) expressed in oocytes or Flp293 cells were used to evaluate the uptake and inhibitory potential of lesinurad sodium upon hOAT1 and hOAT3 kidney transporters. Clinically achievable concentrations of lesinurad sodium were not capable of inhibiting hOAT1 and hOAT3 in these assays (21).

These studies support the hypothesis that the likely mechanism for RDEA-806 to reduce sUA is due to increased urinary excretion of uric acid.

PHARMACOKINETICS AND METABOLISM

Allopurinol, its active metabolite oxypurinol and febuxostat are xanthine oxidase inhibitors used to treat gout. Because they have a different mechanism of action for reducing sUA levels, they could potentially be used in combination with lesinurad sodium to decrease sUA levels when either agent alone is not sufficient. In Sprague-Dawley rats, lesinurad sodium or febuxostat alone was dosed orally for 3 days before beginning concomitant administration of the other compound on day 4. The pharmacokinetics of febuxostat or lesinurad sodium following coadministration were then compared to rats receiving monotherapy with either febuxostat or lesinurad sodium. In male and female Sprague-Dawley rats, coadministration of lesinurad sodium and febuxostat did not alter the pharmacokinetics of either agent (22).

In male cynomolgus monkeys, a two-period, one-way crossover study was conducted with oral administration followed by plasma and urine collection. In period 1, a single dose of either lesinurad sodium (group 1) or allopurinol (group 2) was administered. In period 2, lesinurad sodium was administered concomitantly with allopurinol (group 1) or allopurinol concomitantly with lesinurad sodium (group 2). In an add-on period 3, probenecid was administered concomitantly with allopurinol. Lesinurad sodium had no effect on the plasma pharmacokinetics or urinary excretion of allopurinol in monkeys. The pharmacokinetics and urinary excretion of allopurinol and oxypurinol, however, were significantly altered by coadministration of probenecid (22).

In humans, the pharmacokinetics of lesinurad sodium have been studied in both healthy and renally impaired subjects. Fasting and fed healthy volunteers aged 18-45 years were given ascending single (5-600 mg) and multiple (100-400 mg) doses of lesinurad sodium. Mean maximum plasma concentrations occurred approximately 1 hour after oral dosing. Oral clearance was constant across the dose range. A total of 20-50% was excreted unchanged in the urine within 24 hours. Subjects given single doses of 400-600 mg had a 27-31% range of reduction in 24-hour sUA from baseline, and those given multiple doses of 100-200 mg had a 15-30% range of reduction in 24-hour sUA from baseline. Further studies revealed that immediate-release capsules in the fed state produced the best plasma concentration and the greatest mean sUA change of 30-35% (23).

Subjects with normal, mild and moderate renal impairment participated in an open-label, single-dose study and were administered 200 mg of lesinurad sodium. Subjects with moderate to severe renal impairment had plasma AUC values that were more variable and sometimes moderately higher than in subjects with mildly impaired or normal renal function. Renal clearance of lesinurad was reduced when creatinine clearance was < 40 mL/min, whereas total oral clearance was less affected. Protein binding did not differ across renal function categories. Urinary urate excretion and urate clearance were increased from baseline in subjects with normal renal function and mild to moderate renal impairment following a single 200-mg dose of lesinurad sodium (24).

In another study, untreated gout subjects with normal, mild and moderate renal impairment participated in a double-blind, placebo-controlled study in which they received lesinurad sodium 200, 400 or 600 mg or placebo. There was no difference in plasma trough levels of lesinurad and sUA-lowering effect across the renal function categories following treatment with the different doses of lesinurad sodium (24).

A similar study was carried out in gout subjects with inadequate response to allopurinol 200-600 mg/day. In these subjects, lesinurad sodium (200, 400 and 600 mg) or placebo was administered in addition to their stable background allopurinol dose. Only a small increase in trough concentrations of lesinurad sodium was observed in subjects with mild to moderate renal impairment. In this study, there were too few subjects with creatinine clearance < 60 mL/min for independent analysis (24).

In two open-label, double-blind, placebo-controlled studies, untreated gout subjects with hyperuricemia received allopurinol 300 mg and lesinurad sodium 200-600 mg daily. Lesinurad had a minimal effect on plasma levels of allopurinol and mildly reduced plasma levels of oxypurinol; however, there was little impact on the functional activity

of xanthine oxidase inhibition on 24-hour urinary xanthine and hypoxanthine excretion. Allopurinol did not change the pharmacokinetics of lesinurad sodium (< 25%) and lesinurad sodium did not alter the pharmacokinetics of allopurinol (< 25%) (25).

In another combination study of lesinurad sodium with stable allopurinol doses in renally impaired subjects, the pharmacokinetics of lesinurad sodium were not affected by moderate (creatinine clearance ≥ 30 to < 60 mL/min) renal impairment (26).

SAFETY

In a study in 98 healthy volunteers given 5-600 mg lesinurad sodium, subjects experienced mild to moderate adverse events consisting of abdominal pain, constipation, diarrhea, headache and oropharyngeal pain. There were no serious events, deaths or premature discontinuations due to adverse events. There were no clinically significant changes in physical examination, vital signs, ECG or laboratory values (other than reduction in sUA) (23).

Lesinurad sodium was well tolerated in combination with allopurinol in 3 studies in a total of 319 subjects (24). There were no serious adverse events or discontinuations due to adverse events. No subjects had a gout flare. There were no clinically significant changes in ECG, vital signs or laboratory values, except for the desired reduction in sUA. No subjects had a grade 1 increase in serum creatinine level. 24-Hour undissociated urine urate was well below 20 mg/dL for allopurinol alone and in combination with lesinurad sodium, suggesting that these subjects are not at risk for renal stones. On allopurinol alone, two patients reported gout flares and two patients withdrew from the study early due to an adverse event, including one patient with acute coronary syndrome and one patient with a moderate gout flare (26).

Lesinurad sodium was also well tolerated in 35 normal healthy subjects in combination with febuxostat. Adverse events were mild to moderate in severity, and no clinically significant changes were observed in ECG, physical examination or vital signs. In three subjects, increases in ALT were noted at the time they were receiving febuxostat alone or in combination with lesinurad sodium, but the current assessment suggests they were not adverse events (27).

CLINICAL STUDIES

A two-way, crossover, two-period, two-panel study was conducted in healthy adult subjects administered RDEA-806 or lesinurad sodium and emtricitabine plus tenofovir (Truvada®), which are reverse transcriptase inhibitors dependent on OAT1 and OAT3 for renal excretion. RDEA-806 and lesinurad sodium had no effect on the plasma pharmacokinetics of Truvada®, nor did Truvada® affect the pharmacokinetics of RDEA-806 or lesinurad sodium. Neither RDEA-806 nor lesinurad sodium inhibited OAT1 or OAT3 (21).

Several combination studies with lesinurad sodium and xanthine oxidase inhibitors have been conducted.

A study in gout patients on allopurinol 300 mg alone or in combination with lesinurad sodium (400 or 600 mg) demonstrated that 100% met the target sUA (< 6 mg/dL) reduction in 7 days with combination therapy compared to 27% on allopurinol alone. Mean sUA change from baseline was 40% with allopurinol alone and 50% and 60%, respectively, with combination allopurinol and lesinurad sodium 400 or 600 mg. Combination of lesinurad sodium and allopurinol achieved an sUA < 6 mg/dL in all 11 subjects (100%), an sUA < 5 mg/dL in all 5 subjects (100%) at a dose of lesinurad sodium of 600 mg and 67% at a dose of lesinurad sodium of 400 mg, and an sUA < 4 mg/dL in 60% at a dose of lesinurad sodium of 600 mg (25, 26).

In a double-blind, placebo-controlled, crossover study in healthy volunteers with sUA > 6 mg/dL, panel 1 received lesinurad sodium 200 mg and panel 2 received lesinurad sodium 400 mg, both alone and in combination with febuxostat 40 mg. When administered as a single agent, lesinurad sodium reduced sUA by 40% at 200 mg and by 50% at 400 mg from baseline compared to a 45% reduction with febuxostat 40 mg over 7 days. The combination of febuxostat and lesinurad sodium reduced sUA by 60% at 200 mg lesinurad sodium and by 70% at 400 mg lesinurad sodium from baseline in 7 days (27).

In a study in 21 gout patients with sUA > 8 mg/dL, patients received 40 or 80 mg febuxostat daily. Lesinurad sodium 400 mg was added to both groups and then increased to 600 mg daily. After 7 days, 100% of patients receiving the combination of lesinurad and febuxostat achieved sUA below 6 mg/dL, compared to 67% and 56%, respectively, for febuxostat 40 and 80 mg. At the highest combination doses tested (600 mg of lesinurad sodium and 80 mg of febuxostat), 100% of subjects achieved sUA levels < 4 mg/dL. No patients achieved these reduced sUA levels on either dose of febuxostat alone. The combination of low-dose febuxostat 40 mg and lesinurad sodium 400 mg ($P < 0.05$) was significantly better than the high dose of febuxostat (80 mg) alone (no P value reported) (28).

DRUG INTERACTIONS

There were no clinically relevant drug–drug interactions between lesinurad sodium and allopurinol in 43 gout patients or between lesinurad sodium and febuxostat in 36 healthy subjects or 21 gout patients at the doses tested (25-28).

SOURCE

Ardea Biosciences, Inc. (US).

DISCLOSURES

The author states no conflicts of interest.

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