HYPERTENSION AND HYPERURICEMIA

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 61/489,597, filed May 24, 2011, which application is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Hypertension is treated with anti-hypertensive agents such as thiazide diuretics, which may elevate serum uric acid levels.

SUMMARY OF THE INVENTION

[0003] In one aspect, there is provided use of lesinurad in combination with allopurinol in the manufacture of a medicament for treating gout in a patient on concomitant thiazide diuretics.

[0003a] In one aspect, there is provided use of an OAT4 inhibitor in combination with allopurinol in the manufacture of a medicament for reducing the incidences of or likelihood of or reversing hyperuricemia or gout in a patient receiving thiazide treatment.

[0003b] In one aspect, there is provided use of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof in combination with allopurinol in the manufacture of a medicament for reducing or reversing hyperuricemia or gout in a patient receiving hydrochlorothiazide.

[0003c] In one aspect, there is provided use of an OAT4 inhibitor in combination with allopurinol in the manufacture of a medicament for reducing serum uric acid levels in a patient suffering from hypertension, wherein the patient is receiving a thiazide diuretic, and wherein administration of the thiazide diuretic results in elevated serum uric acid levels.

[0003d] In one aspect, there is provided a composition comprising:

i. a thiazide diuretic;
ii. an OAT4 inhibitor;
iii. allopurinol; and
iv. a pharmaceutically acceptable excipient or carrier.

[0003e] In one aspect, there is provided a composition comprising:

i. a thiazide diuretic;
ii. 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof;
iii. allopurinol; and
iv. a pharmaceutically acceptable excipient or carrier.

[0003f] In one aspect, there is provided a composition comprising:

i. hydrochlorothiazide;

ii. 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof;

iii. allopurinol; and

iv. a pharmaceutically acceptable excipient or carrier.

[0003g]Provided in certain embodiments herein is a method for treating hypertension in a subject in need thereof (e.g., wherein said treatment does not result in an increase in serum uric acid levels, does not result in abnormally elevated serum uric acid levels, does not result in hyperuricemia, does not result in serum uric acid levels of above 6 mg/dL, or does not result in the development of gout in the subject), the method comprising administering to the subject:

a. a thiazide diuretic; ~~and~~

b. an organic anion transporter 4 (OAT4) inhibitor; and~~.~~

c. allupurinol

[0004] In some embodiments, the thiazide diuretic is selected from hydrochlorothiazide, bendroflumethiazide, benzothiadiazine, hydroflumethiazide, clorothiazide, methyclothiazide, polythiazide, chlorthalidone, metolazone, indapamide, bumetanide, ethacrynic acid, furosemide or torsemide.

[0005] In certain embodiments, the OAT4 inhibitor is 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof.

[0006] In some embodiments, any method described herein further comprises administering a URAT1 inhibitor to the subject. In specific embodiments, the OAT4 inhibitor and the URAT1 inhibitor are the same drug.

[0007] Provided in some embodiments herein is a method for treating hypertension in a subject in need thereof, wherein said treatment does not result in an increase in serum uric acid levels, comprising administering to the subject:

a. hydrochlorothiazide; ~~and~~

b. 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof; and

c. allopurinol.

[0008] Provided in some embodiments herein is a method of reducing serum uric acid, treating gout, or reducing the incidences of elevated serum uric acid or gout in a subject suffering from hypertension, the method comprising administering an OAT4 inhibitor, such as an OAT4 inhibitor described herein. In specific embodiments, the elevated serum uric acid or gout is induced by the administration of a thiazide. In certain embodiments, provided herein is a method of treating an OAT4 mediated disorder in a subject by administering to the subject 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid, a pharmaceutically acceptable salt thereof, or an anlalog thereof. In specific embodiments, the OAT4 mediated disorder is OAT4 mediated hyperuricemia or OAT4 mediated gout.

[0009] In some embodiments, provided herein is a method for reducing the incidences of or likelihood of or reversing the diagnosis of hyperuricemia or gout in a patient receiving thiazide treatment, comprising administering an OAT4 inhibitor and allopurinol to the patient.

[0010] In certain embodiments, provided herein is a method for reducing serum uric acid levels in a patient suffering from hypertension, comprising administering to the subject an effective amount of an OAT-4 inhibitor and allopurinol, wherein the patient is receiving a thiazide diuretic, and wherein (absent the administration of the OAT-4 inhibitor) administration of the thiazide diuretic results in elevated serum uric acid levels.

[0011] In some embodiments, provided herein is a composition comprising:

a. a thiazide diuretic;

b. an OAT-4 inhibitor; ~~and~~

c. allopurinol; and

~~e~~d. a pharmaceutically acceptable excipient or carrier.

[0012] In specific embodiments, provided herein is a composition comprising:

a. hydrochlorothiazide;

b. 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof; ~~and~~

c. allopurinol; and

~~e~~d. a pharmaceutically acceptable excipient or carrier.

INCORPORATION BY REFERENCE

[0013] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

WHAT IS CLAIMED IS:,

1. Use of lesinurad in combination with allopurinol in the manufacture of a medicament for treating gout in a patient on concomitant thiazide diuretics.
2. The use of claim 1, wherein a dose of lesinurad is 200 mg.
3. The use of claim 1, wherein a dose of lesinurad is 400 mg.
4. Use of an OAT4 inhibitor in combination with allopurinol in the manufacture of a medicament for reducing the incidences of or likelihood of or reversing hyperuricemia or gout in a patient receiving thiazide treatment.
5. The use of claim 4, wherein the OAT4 inhibitor is 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof.
6. The use of claim 4, wherein the thiazide treatment is treatment with hydrochlorothiazide, bendroflumethiazide, benzothiadiazine, hydroflumethiazide, chlorothiazide, methyclothiazide, polythiazide, chlorthalidone, metolazone, indapamide, bumetanide, ethacrynic acid, furosemide or torsemide.
7. Use of 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof in combination with allopurinol in the manufacture of a medicament for reducing or reversing hyperuricemia or gout in a patient receiving hydrochlorothiazide.
8. Use of an OAT4 inhibitor in combination with allopurinol in the manufacture of a medicament for reducing serum uric acid levels in a patient suffering from hypertension, wherein the patient is receiving a thiazide diuretic, and wherein administration of the thiazide diuretic results in elevated serum uric acid levels.
9. The use of claim 8, wherein the OAT4 inhibitor is 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof.
10. A composition comprising:
    i. a thiazide diuretic;
    ii. an OAT4 inhibitor;
    iii. allopurinol; and
    iv. a pharmaceutically acceptable excipient or carrier.
11. A composition comprising: