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(54) Title: CO-FORMULATIONS OF KITS OF BIOACTIVE AGENTS

(57) Abstract: Provided, among other things, is a formulation or kit comprising: (a) a pharmaceutically effective dosage of one or more a glucose-level-controlling bioactive agents selected from an α-glucodase inhibitor, sulfonylurea, meglitinide, thiazolidinediones, biguanide, insulin, dual PPAR α/γ agonist, PPARγ agonist or insulin secretagogue; and (b) a pharmaceutically effective dosage of (i) one or more of an antihypertensive bioactive agent selected from an ACE inhibitor, calcium channel blocker, beta blocker, angiotension II receptor antagonist or diuretic, or (ii) one or more of an anti-dyslipidemia bioactive agent selected from a HMG-CoA reductase inhibitor, bile acid sequestrant, fabric acid derivative, sterol, cholesterol absorption inhibitor, MTP inhibitor or nicotinic acid derivative; wherein: in the case of (i) a combination of a first bioactive agent of group (a) that is metformin with a second bioactive agent of group (b), or (ii) a combination of a first bioactive agent of group (a) that is a thiazolidinedione or dual PPAR α /γ agonist with an angiotension II receptor antagonist, one or more of the following applies: (I) one of the first bioactive agent or the second bioactive agent is formulated for sustained release, and the other is formulated for immediate release, each formulated for once-a-day dosing; or (II) the co-formulation or kit comprises (A) a biguanide and a thiazolidinedione and (B) one or more group (b) bioactive agents.

Co-formulations or Kits of Bioactive Agents

[1] The present invention relates to the use of multi-bioactive agent administration products having two or more different bioactive agents indicated for two or more different disease conditions to an individual in need of such bioactive agents. More specifically, the invention relates to co-formulations or kits of two or more different bioactive agents for treating diabetes and its co-morbidities (including co-existing disease conditions), including hypertension, dyslipidemia, cardiovascular disease, and nephropathy

[2] According to studies cited in Merck Manual, only about half of patients who leave a physician's office with a prescription take the medicament as directed. The most common reason given for noncompliance is forgetfulness. Other reasons for noncompliance with medicament regimens include lack of understanding or confusion about dosing. Older persons with cognitive impairment often find the dosing regimen complex, and difficult to remember and to follow.

[3] Current therapeutic regimens for individuals having two or more separate disease conditions typically involve treatment with two or more different and distinct bioactive agents, which often need to be given at separate times. The individuals need to take each bioactive agent at its required time for maximum therapeutic effect. Individuals who must take multiple bioactive agents on multiple schedules to treat more than one disease condition often find this multi-bioactive agent administration regimen very confusing and even more difficult to follow. Multi-bioactive agent administration is especially difficult for elderly patients who often have several co-existing conditions needing therapeutic treatment.

[4] Various solutions have been suggested for improving patient compliance with medication dosing, including intervention by the physician and/or pharmacist. However, it is generally accepted that the best possible dosing regimen for patient compliance is a simplified regimen, especially a once-daily dosing regimen.

[5] There is recent evidence based on prospective and retrospective analysis that comorbidity of hyper-lipidemia and diabetes is prevalent and could benefit from concomitant treatment with an anti-dyslipidemia agent and a glucose controlling agent.

[6] Co-administration of these bioactive agents however is often difficult since the glucose lowering agent often needs to be dosed multiple times a day and the anti-dyslipidemia agent is typically administered once a day, preferably at night time. A single administration of anti-diabetic bioactive agent can be achieved by formulating the bioactive agent in a sustained release dosage form. However, addition of the anti-dyslipidemia agent in the same sustained release dosage form could inappropriately control the second bioactive agent's release such that it would be difficult to achieve therapeutic levels.

[7] United States Patent 6,660,300 to Timmins et al describes a delivery system wherein Metformin and optionally a hypolipidemic agent are administered in a biphasic system. The delivery system's two phases are: an inner solid particulate phase of granules containing a highly water soluble pharmaceutical with hydrophilic and hydrophobic polymers, and an outer solid continuous phase in which the inner solid particulate phase granules are dispersed. The outer solid continuous phase is formed of an extended release material with hydrophobic polymers or materials. Since both phases in the described system contain hydrophobic polymers, it is likely to control the release of not only highly soluble Metformin which requires an extended release profile, but will also inhibit the release of any hypolipidemic agent, leading to sub-therapeutic levels of the hypolipidemic agent.

[8] WO 2004/017896 A2, to Waldstreicher et al, describes a combination bioactive agent therapy for the treatment of hypertension and type 2 diabetes mellitus, Metabolic Syndrome, or a pre-diabetic condition in a patient in need of such treatment. The invention describes the use of combinations of pharmaceutically active compounds that are dual agonists of the alpha and gamma subtypes of the peroxisome proliferators activated receptor (PPARα/γ) with Angiotensin II Type I receptor (A-2) antagonists. The invention does not specifically address the combinations of other bioactive agents for treatment of diabetes and comorbidities, particularly where the bioactive agents have distinct treatment regimens.

[9] What is needed then is a multi-bioactive agent administration product for concurrently treating two distinct disease conditions each of which has distinct treatment options and different treatment regimens.

Summary of the Invention

[10] Provided, among other things, is a formulation or kit comprising:

(a) a pharmaceutically effective dosage of one or more a glucose-level-controlling bioactive agents selected from an α-glucodase inhibitor, sulfonylurea, meglitinide, thiazolidinediones, biguanide, insulin, dual PPARα/γ agonist, PPARγ agonist or insulin secretagogue; and

(b) a pharmaceutically effective dosage of (i) one or more of an antihypertensive bioactive agent selected from an ACE inhibitor, calcium channel blocker, beta blocker, angiotension II receptor antagonist or diuretic, or (ii) one or more of an anti-dyslipidemia bioactive agent selected from a HMG-CoA reductase inhibitor, bile acid sequestrant, fibric acid derivative, sterol, cholesterol absorption inhibitor, MTP inhibitor or nicotinic acid derivative;

wherein:

in the case of (i) a combination of a first bioactive agent of group (a) that is metformin with a second bioactive agent of group (b), or (ii) a combination of a first bioactive agent of group (a) that is a thiazolidinedione or dual PPARα/γ agonist with an angiotension II receptor antagonist, one or more of the following applies:

(I) one of the first bioactive agent or the second bioactive agent is formulated for sustained release, and the other is formulated for immediate release, each formulated for once-a-day dosing; or

(II) the co-formulation or kit comprises (A) a biguanide and a thiazolidinedione and (B) one or more group (b) bioactive agents.

[11] The multi-bioactive agent administration product may be a co-formulation or a kit. The kit may comprise, for example, daily dosing for 7, 14, 21, 28 or more days.

[12] In certain embodiments, such a co-formulation is a capsule wherein

one or more group (a) bioactive agents are formulated in sustained release beads comprised within the capsule; and

one or more group (b) bioactive agents in a more immediate release form are comprised within the capsule.

[13] In certain embodiments, such a co-formulation is a compression formulation wherein

one or more group (a) bioactive agents are formulated in sustained release form comprised within a portion of the compression formulation; and

one or more group (b) bioactive agents in a more immediate release form are comprised within another portion of the compression formulation.

[14] In certain embodiments, such a co-formulation is a suspension formulation wherein

one or more group (a) bioactive agents are formulated in sustained release form comprised within particles that are suspended or adapted to be suspended in a liquid; and

one or more group (b) bioactive agents are dissolved in the liquid.

The instructions for the co-formulation may provide that it should be shaken immediately prior to use (to suspend particles). Particles may be beads, such as described below. Bead and liquid density can be selected to increase bead propensity to remain in suspension.

[15] In certain embodiments the invention provides, among other things, methods of treating diabetes or its co-morbidities. One such method is for delivering in the co-formulation a glucose-level-controlling bioactive agent and a second bioactive agent for treating a co-morbidity of diabetes, the glucose-level-controlling bioactive agent having a first dosing regimen and the second bioactive agent having a second, distinct dosing regimen, wherein the co-formulation provides a pharmacokinetic profile of the glucose-level-controlling bioactive agent that mimics the first dosing regimen and a pharmacokinetic profile of the second bioactive agent that mimics the second dosing regimen.

Brief Description of the Drawings

[16] **Figure 1** is an embodiment of a kit of the invention.

[17] **Figure 2** is another embodiment of a kit of the invention.

[18] **Figure 3** is a further embodiment of a kit of the invention.

[19] **Figure 4** shows diesolution profiles of formulations of the invention.

Detailed Description of the Invention

Dual Release Embodiments

DOCKET ALARM

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