PHARMACEUTICAL COMPOSITIONS COMPRISING METFORMIN AND A DPP-4 INHIBITOR OR A SGLT-2 INHIBITOR

The present disclosure relates to pharmaceutical compositions containing a fixed dose combination (FDC) comprising
a DPP-4 inhibitor drug (particularly 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, also named linagliptin) and/or
a SGLT-2 inhibitor drug (particularly 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene, also named Compound "A" herein),
and
metformin (particularly metformin hydrochloride) in extended release form (metformin XR);
processes for the preparation thereof, and their use to treat certain diseases.

In particular, the present disclosure relates to a pharmaceutical composition comprising a fixed dose combination of an extended release form of metformin hydrochloride, optionally seal or barrier coated, which is further coated with an immediate release form of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine (linagliptin) and/or 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene (Compound "A").

In a first aspect, there is provided a pharmaceutical composition comprising

a) an extended release core comprising ~~metformin (particularly~~ metformin hydrochloride,~~)~~ poly(ethylene oxide) as a swellable and/or extended release polymer, and one or more excipients;
b) ~~an optional seal and/or~~ barrier coating comprising a mixture of hydroxypropyl cellulose and hydroxypropyl methylcellulose as film-coating agent; and
c) an immediate release coating comprising:~~at least one active pharmaceutical ingredient selected from~~
~~a DPP-4 inhibitor, preferably~~ linagliptin, L-arginine as stabilizer, a plasticizer which is polyethylene glycol, a film-coating agent which is hydroxypropyl methylcellulose, and a glidant which is talc~~and~~
~~a SGLT-2 inhibitor, preferably 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene~~,
~~and one or more excipients~~.

Further, the present disclosure relates to a pharmaceutical composition, particularly a solid preparation (e.g. an oral solid dosage form, such as e.g. a tablet), comprising or consisting essentially of

a) an inner extended release core comprising metformin (particularly metformin hydrochloride) and one or more excipients;
b) an optional intermediate seal and/or barrier coating; and
c) an outer immediate release coating comprising at least one active pharmaceutical ingredient selected from
a DPP-4 inhibitor, preferably linagliptin, and
a SGLT-2 inhibitor, preferably Compound "A",
and one or more excipients.

In more detail, the present disclosure relates to a pharmaceutical composition, particularly a solid preparation (e.g. an oral solid dosage form, such as a tablet) of a selected dipeptidyl peptidase-4 (DPP-4) inhibitor (preferably linagliptin, particularly in immediate release form) and metformin (particularly metformin hydrochloride) in extended release form (metformin XR). In one embodiment, the present disclosure relates to a

Optionally, the pharmaceutical compositions, particularly solid preparations (e.g. oral solid dosage forms, such as e.g. tablets) according to the present disclosure may further comprise a color coat and/or a final coat.

In a second aspect, there is provided use of the pharmaceutical composition as defined herein for preparing a medicament for use in treating and/or preventing (including slowing the progression and/or delaying the onset) of metabolic diseases, especially type 2 diabetes mellitus and conditions related thereto (e.g. diabetic complications), either in type 2 diabetes patients who have not been previously treated with an antihyperglycemic agent, or in type 2 diabetes patients with insufficient glycemic control despite therapy with one or two conventional antihyperglycemic agents selected from metformin, sulphonylureas, thiazolidinediones (e.g. pioglitazone), glinides, alpha-glucosidase blockers, GLP-1 or GLP-1 analogues, and insulin or insulin analogues.

(a) Metformin part:
The first part in the present invention is a part (composition, particularly solid composition, e.g. a solid pharmaceutical composition for oral administration, e.g. tablet) comprising metformin (particularly metformin hydrochloride) in extended release form, particularly an extended release formulation of metformin.

In an embodiment, this first part is a metformin (e.g. 500 mg, 750 mg or 1000 mg metformin hydrochloride) extended release core.

Exemplary extended release formulations of metformin are disclosed in US 6,340,475; US 6,488,962; US 6,635,280; US 6,723,340; US 7780987; US 6,866,866; US 6,495,162; US 6,790,459; US 6,866,866; US 6,475,521; and US 6,660,300; the disclosures of which are incorporated herein in their entireties.

A particular extended release formulation of metformin is described in US 6,723,340, the disclosure of which is incorporated herein in its entirety.

In an embodiment, the fixed-dose combination products of the present invention comprise - as first part - an inner core matrix formulation with metformin hydrochloride dispersed therein, said matrix formulation containing an extended release material. The matrix formulation is compressed into a tablet form.

In a particular embodiment, the fixed-dose combination products of the present invention comprise - as first part - an inner core extended release formulation comprising metformin

Claims:

1. A pharmaceutical composition comprising

a) an extended release core comprising ~~metformin (particularly~~ metformin hydrochloride~~)~~, poly(ethylene oxide) as a swellable and/or extended release polymer, and one or more excipients;

b) a~~n optional seal and/or~~ barrier coating comprising a mixture of hydroxypropyl cellulose and hydroxypropyl methylcellulose as film-coating agent; and

c) an immediate release coating comprising~~: at least one active pharmaceutical ingredient selected from~~

~~a DPP-4 inhibitor, preferably linagliptin, and~~

~~a SGLT-2 inhibitor, preferably 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene,~~

~~and one or more excipients~~

linagliptin,

L-arginine as stabilizer,

a plasticizer which is polyethylene glycol,

a film-coating agent which is hydroxypropyl methylcellulose, and

a glidant which is talc.

~~2. The pharmaceutical composition according to claim 1, wherein the inner extended release core a) is a formulation comprising metformin hydrochloride, a swellable and/or extended release polymer, and one or more further excipients.~~

~~3. The pharmaceutical composition according to claim 1 or 2, wherein the immediate release coating c) is a film-coat formulation comprising~~

~~the at least one active pharmaceutical ingredient, preferably a stabilizer for stabilizing linagliptin (preferably L-arginine), and~~

~~one or more film-coating agents selected from hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), ethyl cellulose, hydroxypropyl cellulose, polydextrose, methacrylic and/or acrylic polymer, or a mixture thereof,~~

~~optionally one or more plasticizers selected from polyethylene glycol, propylene glycol, diethyl phthalate, tributyl sebacate and/or triacetin, or a mixture thereof,~~

~~optionally a glidant selected from talc, magnesium stearate and fumed silica, and~~

~~optionally one or more pigments and/or colorants.~~

~~4. The pharmaceutical composition according to claim 1, 2 or 3, wherein the immediate release coating c) is a film coat formulation comprising linagliptin, L-arginine as stabilizer, a film-coating agent, a plasticizer, and, optionally, a glidant.~~

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~~5~~2. The pharmaceutical composition according to claim ~~3 or 4~~ 1, wherein the weight ratio of the L-arginine to linagliptin is within the range from about 4:1 to about 2:1~~, especially about 4:1~~.

~~6. The pharmaceutical composition according to claim 1, 2 or 3, wherein the outer immediate release coating c) is a film coat formulation comprising 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene, a film-coating agent, a plasticizer, and, optionally, a glidant.~~

~~7. The pharmaceutical composition according to claim 3, 4, 5 or 6, wherein the one or more film-coating agents are selected from hydroxypropyl methylcellulose, e.g. hypromellose 2910 with nominal viscosity of 3, 5, 6, 15 and/or 50 cP, Methocel E5, Methocel E15, Pharmacoat 603, Pharmacoat 606 and/or Pharmacoat 615.~~

~~8. The pharmaceutical composition according to claim 3, 4, 5, 6 or 7, wherein the one or more plastizicers are selected from polyethylene glycol, e.g. Macrogol 400, 3000, 4000, 6000 and/or 8000.~~

~~9. The pharmaceutical composition according to claim 3, 4, 5, 6 or 7, wherein the plasticizer is propylene glycol.~~

~~10. The pharmaceutical composition according to any one of claims 3 to 9, wherein the optional glidant is talc.~~

~~11~~3. The pharmaceutical composition according to any one of claims 1 to ~~5~~2, wherein ~~c) is an~~the immediate release API coating ~~comprising or~~ c) comprises or ~~consisting~~ consists essentially of:

polyethylene glycol of molecular weight of about 6000 ~~(e.g.~~in an amount of 8-20 % w/w~~, preferably 10-18 % w/w, such as 14.0 or 11.9 % w/w)~~,

linagliptin ~~(as API, e.g.~~in an amount of 1-10 % w/w~~, preferably 2-7 % w/w, such as 3.5 or 6.0 % w/w)~~,

L-arginine ~~(as stabilizer, e.g. the weight ratio L-arginine: linagliptin may be 1:1 to 5:1, preferably 2:1 to 4:1, especially 4:1; such as e.g.~~in an amount of 4-40 % w/w~~, preferably 10-30 % w/w, such as 14 or 24 % w/w)~~,

hydroxypropyl methylcellulose (~~e.g. hydroxypropyl methylcellulose of 3 cP, e.g.~~in an amount of 40-70 % w/w~~, preferably 40-65 % w/w, such as 53.2 or 45.2 % w/w)~~,

polyethylene glycol of molecular weight of about 8000 ~~(e.g.~~in an amount of 0-5 % w/w~~, preferably 2-4 % w/w, such as 2.8 or 2.4 % w/w)~~, and

talc ~~(e.g.~~in an amount of 5-20 % w/w~~, preferably 8-16 % w/w, such as 12.5 or 10.7 % w/w)~~,

wherein % w/w relate to the weight of the immediate release coating, and

wherein the content of linagliptin ~~may be~~is in the range from 1 to 10 mg~~, particularly 2.5 mg or 5.0 mg~~.

~~12. The pharmaceutical composition according to any one of the claims 1 to 11, wherein the seal coating is present and/or the barrier coating is present.~~

~~13~~4. The pharmaceutical composition according to any one of claims ~~12~~1 to 3, wherein the ~~seal and/or~~ barrier coating is ~~each~~ a film coat formulation ~~independently~~ further comprising:
~~one or more film-coating agents selected from hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), ethyl cellulose, hydroxypropyl cellulose, polydextrose, methacrylic and/or acrylic polymer, or a mixture thereof,~~
optionally one or more plasticizers selected from polyethylene glycol, propylene glycol, diethyl phthalate, tributyl sebacate and/or triacetin, or a mixture thereof,
optionally a glidant selected from talc, magnesium stearate and fumed silica, and
optionally one or more pigments and/or colorants.

~~14~~5. The pharmaceutical composition according to claim ~~12 or 13~~any one of claims 1 to 4, wherein the ~~seal and/or~~ barrier coating is ~~each~~ a film coat formulation ~~independently~~ further comprising ~~a film-coating agent,~~ a plasticizer, and, optionally, a glidant, one or more pigments and/or colors.

~~15. The pharmaceutical composition according to claim 12, 13 or 14, wherein the seal and/or barrier coat comprises~~
~~a film-coating agent which is hydroxypropyl methylcellulose (HPMC, hypromellose such as e.g. Methocel E5, or Pharmacoat 606),~~
~~a plasticizer which is triacetin, and~~
~~a glidant which is talc, and~~
~~optionally one or more pigments and/or colors.~~

~~16. The pharmaceutical composition according to claim 12, 13, 14 or 15, wherein the seal and/or barrier coat comprises~~
~~one or more film-coating agents selected from hydroxypropyl methylcellulose (HPMC, hypromellose such as e.g. hypromellose 2910 with nominal viscosity of 3 cP, hypromellose 2910 with nominal viscosity of 5 cP, hypromellose 2910 with nominal viscosity of 6 cP, hypromellose 2910 with nominal viscosity of 15 cP, hypromellose 2910 with nominal viscosity~~

~~of 50 cP, Methocel E5, Methocel E15, Pharmacoat 603, Pharmacoat 606, and/or Pharmacoat 615), and polydextrose, or mixtures thereof,~~
~~a plasticizer selected from polyethylene glycol (such as e.g. Macrogol 400, 3000, 4000, 6000 or 8000), and~~
~~optionally one or more pigments (e.g. titanium dioxide) and/or colors.~~

~~17. The pharmaceutical composition according to claim 12, 13, 14, 15 or 16, wherein the seal and/or barrier coat comprises~~
~~a mixture of one or more hydroxypropyl methylcellulose (HPMC, hypromellose 2910 with nominal viscosity of 3 cP, hypromellose 2910 with nominal viscosity of 6 cP, and hypromellose 2910 with nominal viscosity of 50 cP) and polydextrose,~~
~~a plasticizer which is polyethylene glycol 8000, and~~
~~optionally one or more pigments (e.g. titanium dioxide) and/or colors.~~

~~18~~6. The pharmaceutical composition according to any one of the preceding claims, wherein the metformin hydrochloride is present in an unit dosage strength of 500, 750, 850, 1000 or 1500 mg.

~~19. The pharmaceutical composition according to any one of the claims 1 to 11, wherein b) is present and is a barrier coating comprising or consisting essentially of:~~
~~polydextrose, hydroxypropyl methylcelluloses (e.g. 3 to 50 cP, such as HPMC 2910-3, HPMC 2910-6 and HPMC 2910-50), titanium dioxide and polyethylene glycol (e.g. PEG 8000), and wherein the barrier coating may have a weight in the range from 50 to 100 mg (such e.g. 68 mg or 85 mg).~~

~~20~~7. The pharmaceutical composition according to any one of the preceding claims, wherein the linagliptin is present in an unit dosage strength of 0.5, 1, 2.5 or 5 mg.

8. The pharmaceutical composition according to any one of the preceding claims, wherein the weight ratio of the L-arginine to linagliptin is about 4:1.

~~21. The pharmaceutical composition according to any one of the preceding claims, wherein the 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene is present in an unit dosage strength of 5, 10, 12.5 or 25 mg.~~

~~22~~9. The pharmaceutical composition according to any of the preceding claims, which is in the form of a tablet for oral administration.

~~23~~10. The tablet according to claim ~~22~~ 9 further comprising a color and/or final coating.

~~24~~11. The tablet according to claim ~~23~~10, wherein the color and/or final coating is each a film coat formulation independently comprising
one or more film-coating agents selected from hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), ethyl cellulose, hydroxypropyl cellulose, polydextrose, methacrylic and/or acrylic polymer, or a mixture thereof,
optionally one or more plasticizers selected from polyethylene glycol, propylene glycol, diethyl phthalate, tributyl sebacate and/or triacetin, or a mixture thereof,
optionally a glidant selected from talc, magnesium stearate and fumed silica, and
optionally one or more pigments (e.g. titanium dioxide) and/or colorants.

~~25~~12. The tablet according to claim ~~23~~ 10 or ~~24~~11, wherein the color and/or final coating is each a film coat formulation independently comprising a film-coating agent, a plasticizer, and, optionally, a glidant, one or more pigments and/or colors.

~~26~~13. Use of ~~The~~ the pharmaceutical composition according to any one of ~~the preceding~~ claims 1 to 9 ~~for preparing a medicament~~ for use in treating and/or preventing (including slowing the progression and/or delaying the onset) of metabolic diseases, especially type 2 diabetes mellitus and conditions related thereto (e.g. diabetic complications),
either in type 2 diabetes patients who have not been previously treated with an antihyperglycemic agent,
or in type 2 diabetes patients with insufficient glycemic control despite therapy with one or two conventional antihyperglycemic agents selected from metformin, sulphonylureas, thiazolidinediones (e.g. pioglitazone), glinides, alpha-glucosidase blockers, GLP-1 or GLP-1 analogues, and insulin or insulin analogues.

~~27~~14. The ~~pharmaceutical composition for~~ use according to claim ~~26~~13, wherein linagliptin is comprised in an amount of 2.5 mg, and metformin hydrochloride is comprised in an amount of 750 mg or 1000 mg ~~in the composition.~~

~~28~~15. The ~~pharmaceutical composition for~~ use according to claim ~~27~~14, wherein the composition is administered as two tablets once daily to the patients.

~~29~~16. The ~~pharmaceutical composition for~~ use according to claim ~~26~~13, wherein linagliptin is comprised in an amount of 5 mg, and metformin hydrochloride is comprised in an amount of 1000 mg~~.~~ in the composition.

~~30~~17. The ~~pharmaceutical composition for~~ use according to claim ~~29~~16, wherein the composition is administered as one tablet once daily to the patients.