Aim of the present invention

The aim of the present invention is to provide a pharmaceutical composition and method for preventing, slowing progression of, delaying or treating a metabolic disorder, in particular of type 2 diabetes mellitus.

A further aim of the present invention is to provide a pharmaceutical composition and method for improving glycemic control in a patient in need thereof, in particular in patients with type 2 diabetes mellitus.

Another aim of the present invention is to provide a pharmaceutical composition and method for improving glycemic control in a patient with insufficient glycemic control.

Another aim of the present invention is to provide a pharmaceutical composition and method for preventing, slowing or delaying progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or metabolic syndrome to type 2 diabetes mellitus.

Yet another aim of the present invention is to provide a pharmaceutical composition and method for preventing, slowing progression of, delaying or treating of a condition or disorder from the group consisting of complications of diabetes mellitus.

A further aim of the present invention is to provide a pharmaceutical composition and method for reducing the weight or preventing an increase of the weight in a patient in need thereof.

Another aim of the present invention is to provide a pharmaceutical composition with a high efficacy for the treatment of metabolic disorders, in particular of diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), and/or hyperglycemia, which has good to very good pharmacological and/or pharmacokinetic and/or physicochemical properties.

Further aims of the present invention become apparent to the one skilled in the art by description hereinbefore and in the following and by the examples.

Summary

Within the scope of the present disclosure it has now surprisingly been found that a pharmaceutical composition comprising a SGLT2 inhibitor as defined hereinafter can advantageously be used for preventing, slowing progression of, delaying or treating a

metabolic disorder, in particular for improving glycemic control in patients. This opens up new therapeutic possibilities in the treatment and prevention of type 2 diabetes mellitus, overweight, obesity, complications of diabetes mellitus and of neighboring disease states.

Therefore, in the present disclosure provides a method for preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity, metabolic syndrome and gestational diabetes in a patient in need thereof characterized in that an SGLT2 inhibitor as defined hereinbefore and hereinafter is administered to the patient.

According to the disclosure, there is provided a method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c in a patient in need thereof characterized in that an SGLT2 inhibitor as defined hereinbefore and hereinafter is administered to the patient.

According to an aspect, there is provided a SGLT2 inhibitor 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene for use in a method for improving glycemic control in a patient in need thereof wherein a pharmaceutical composition comprising an amount of 5 mg to 25 mg of the SGLT2 inhibitor is orally administered once daily to the patient.

According to another aspect, there is provided a SGLT2 inhibitor 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene for use in a method for preventing, slowing the progression of, delaying or treating of complications of diabetes mellitus selected from the group consisting nephropathy, retinopathy, neuropathy, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, accute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis in a patient in need thereof wherein a pharmaceutical composition comprising an amount of 5 mg to 25 mg of the SGLT2 inhibitor is orally administered once daily to the patient.

According to another aspect, there is provided a SGLT2 inhibitor 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene for use in a method for reducing the cardiovascular risk in a patient in need thereof wherein a pharmaceutical

composition comprising an amount of 5 mg to 25 mg of the SGLT2 inhibitor is orally administered once daily to the patient.

The pharmaceutical composition according to this disclosure may also have valuable disease-modifying properties with respect to diseases or conditions related to impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or metabolic syndrome.

According to the disclosure, there is provided a method for preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus in a patient in need thereof characterized in that an SGLT2 inhibitor as defined hereinbefore and hereinafter is administered to the patient.

As by the use of a pharmaceutical composition according to this disclosure, an improvement of the glycemic control in patients in need thereof is obtainable, also those conditions and/or diseases related to or caused by an increased blood glucose level may be treated.

According to the disclosure, there is provided a method for preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia,

diabetic foot, arteriosclerosis, myocardial infarction, accute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis, in a patient in need thereof characterized in that an SGLT2 inhibitor as defined hereinbefore and hereinafter is administered to the patient. In particular one or more features of diabetic nephropathy such as hyperperfusion, proteinuria and albuminuria may be treated, their progression slowed or their onset delayed or prevented. The term "tissue ischaemia" particularly comprises diabetic macroangiopathy, diabetic microangiopathy, impaired wound healing and diabetic ulcer. The terms "micro- and macrovascular diseases" and "micro- and macrovascular complications" are used interchangeably in this application.

By the administration of a pharmaceutical composition according to this disclosure and due to the activity of the SGLT2 inhibitor excessive blood glucose levels are not converted to insoluble storage forms, like fat, but excreted through the urine of the patient. In animal models it can be seen that loss of fat accounts for the majority of the observed weight loss whereas no significant changes in body water or protein content are observed. Therefore, no gain in weight or even a reduction in body weight is the result.

According to the disclosure, there is provided a method for reducing body weight and/or body fat, or preventing an increase in body weight and/or body fat, or facilitating a reduction in body weight and/or body fat, in a patient in need thereof characterized in that an SGLT2 inhibitor as defined hereinbefore and hereinafter is administered to the patient.

The pharmacological effect of the SGLT2 inhibitor in the pharmaceutical composition according to this disclosure is independent of insulin. Therefore, an improvement of the glycemic control is possible without an additional strain on the pancreatic beta cells. By an administration of a pharmaceutical composition according to this disclosure a beta-cell degeneration and a decline of beta-cell functionality such as for example apoptosis or necrosis of pancreatic beta cells can be delayed or prevented. Furthermore, the functionality of pancreatic cells can be improved or restored, and the number and size of pancreatic beta cells increased. It may be shown that the differentiation status and hyperplasia of pancreatic beta-cells disturbed by hyperglycemia can be normalized by treatment with a pharmaceutical composition according to this disclosure.

According to the disclosure, there is provided a method for preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of

the functionality of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion in a patient in need thereof characterized in that an SGLT2 inhibitor as defined hereinbefore and hereinafter is administered to the patient.

By the administration of a pharmaceutical composition according to the present disclosure, an abnormal accumulation of ectopic fat, in particular of the liver, may be reduced or inhibited. Therefore, according to the present disclosure, there is provided a method for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of ectopic fat, in particular liver fat, in a patient in need thereof characterized in that an SGLT2 inhibitor as defined hereinbefore and hereinafter is administered to the patient. Diseases or conditions which are attributed to an abnormal accumulation of liver fat are particularly selected from the group consisting of general fatty liver, non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), hyperalimentation-induced fatty liver, diabetic fatty liver, alcoholic-induced fatty liver or toxic fatty liver.

As a result thereof, there is provided a method for maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance in a patient in need thereof characterized in that an SGLT2 inhibitor as defined hereinbefore and hereinafter is administered to the patient.

According to the disclosure, there is provided a method for preventing, slowing progression of, delaying, or treating new onset diabetes after transplantation (NODAT) and/or post-transplant metabolic syndrome (PTMS).

According to the disclosure, there is provided a method for preventing, delaying, or reducing NODAT and/or PTMS associated complications including micro- and macrovascular diseases and events, graft rejection, infection, and death.

The pharmaceutical composition according to the disclosure is capable of facilitating the lowering of serum total urate levels in the patient. Therefore according to the disclosure, there is provided a method for treating hyperuricemia and hyperuricemia-associated conditions, such as for example gout, hypertension and renal failure, in a patient in need thereof. The patient may be a diabetic or non-diabetic patient.

The administration of a pharmaceutical composition increases the urine excretion of glucose. This increase in osmotic excretion and water release and the lowering of urate levels are

beneficial as a treatment or prevention for kidney stones. Therefore in the disclosure, there is provided a method for treating or preventing kidney stones.

According to the disclosure, there is provided a method for treating hyponatremia, water retention and water intoxication. By the administration of the pharmaceutical composition according to this disclosure it may be possible to reverse the effects of hyponatremia, water retention and water intoxication by acting on the kidney to reverse water retention and electrolyte imbalances associated with these diseases and disorders.

According to the disclosure there is provided the use of an SGLT2 inhibitor for the manufacture of a medicament for

- preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity, metabolic syndrome and gestational diabetes; or
- improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c; or
- preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus; or
- preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, accute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis,; or
- reducing body weight and/or body fat, or preventing an increase in body weight and/or body fat, or facilitating a reduction in body weight and/or body fat; or
- preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion; or
- preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of ectopic fat; or

- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance;
- preventing, slowing progression of, delaying, or treating new onset diabetes after transplantation (NODAT) and/or post-transplant metabolic syndrome (PTMS);
- preventing, delaying, or reducing NODAT and/or PTMS associated complications including micro- and macrovascular diseases and events, graft rejection, infection, and death;
- treating hyperuricemia and hyperuricemia associated conditions;
- treating or prevention kidney stones;
- treating hyponatremia;

in a patient in need thereof characterized in that the SGLT2 inhibitor is administered, as defined hereinbefore and hereinafter.

According to another aspect, there is provided use of a SGLT2 inhibitor 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene in the manufacture of a medicament for improving glycemic control in a patient, wherein the medicament comprises an amount of 5 mg to 25 mg of the SGLT2 inhibitor to be orally administered once daily to the patient.

According to another aspect, there is provided use of a SGLT2 inhibitor 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene in the manufacture of a medicament for preventing, slowing the progression of, delaying or treating of complications of diabetes mellitus selected from the group consisting nephropathy, retinopathy, neuropathy, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, accute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis in a patient, wherein the medicament comprises an amount of 5 mg to 25 mg of the SGLT2 inhibitor to be orally administered once daily to the patient.

According to another aspect, there is provided use of a SGLT2 inhibitor 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene in the manufacture of a medicament for reducing the cardiovascular risk in a patient, wherein the medicaement comprises an amount of 5 mg to 25 mg of the SGLT2 inhibitor to be is orally administered once daily to the patient.

According to the disclosure, there is provided the use of a pharmaceutical composition according to the present disclosure for the manufacture of a medicament for a therapeutic and preventive method as described hereinbefore and hereinafter.

Definitions

The term **"active ingredient"** of a pharmaceutical composition according to the present invention means the SGLT2 inhibitor according to the present invention. An "active ingredient is also sometimes referred to herein as an "active substance".

The term **"body mass index"** or **"BMI"** of a human patient is defined as the weight in kilograms divided by the square of the height in meters, such that BMI has units of kg/m^2.

The term **"overweight"** is defined as the condition wherein the individual has a BMI greater than or 25 kg/m^2 and less than 30 kg/m^2. The terms "overweight" and "pre-obese" are used interchangeably.

The term **"obesity"** is defined as the condition wherein the individual has a BMI equal to or greater than 30 kg/m^2. According to a WHO definition the term obesity may be categorized as follows: the term "class I obesity" is the condition wherein the BMI is equal to or greater than 30 kg/m^2 but lower than 35 kg/m^2; the term "class II obesity" is the condition wherein the BMI is equal to or greater than 35 kg/m^2 but lower than 40 kg/m^2; the term "class III obesity" is the condition wherein the BMI is equal to or greater than 40 kg/m^2.