



“NOVEL DRUG DELIVERY SYSTEM ON TYPE 2 DIABETES MELLITUS”

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ABSTRACT

Chronic hyperglycemia and other metabolic disturbances of diabetes mellitus lead to long term tissue and organ damage as well as dysfunctions involving the eye, kidneys, and nervous systems and vascular system. Good glycemic control delays the development and slows the progression of micro- and macro vascular complications. Undesirable side-effects may hamper treatment in those treated with the older medications. There is a need for novel treatment options that can help overcome these difficulties. Sodium glucose co transporter 2 (SGLT2) inhibitors have recently been developed as a novel potential therapeutic option for the treatment of type 2 diabetes. These drugs lower the plasma glucose concentration through inhibition of glucose reuptake in the kidney, independent of insulin secretion and insulin action, with a consequent lower risk of hypoglycemia. A follow-up study shows long-term efficacy and the durability of these effects. SGLT2 inhibitors have the potential to improve insulin resistance.

KEYWORDS: SGLT2 inhibitors, Type 2 Diabetes Mellitus, novel, long term efficacy.

INTRODUCTION

Diabetes mellitus is a group of metabolic disease characterized by hyperglycemia resulting from defects of insulin secretion and / or increased cellular resistance to insulin. Diabetes has mainly two type, first is type 1 insulin dependent [IDDM] and second is Non insulin dependent diabetes mellitus [NIDDM] in type 1 DM which, results from destruction of beta cells in pancreas and type 2 is most common from world wide, and its prevalence is increasing its underlying defects can vary from predominant insulin resistance with relatively insulin deficiency to a predominant insulin secretory defects with insulin resistance. A great deal of heterogeneity exist, and most patients with type 2 DM do not initially require insulin therapy. Mainly it can cure by oral hyperglycemic therapies. Now a days various classes of medication which can be given in the treatment of diabetes mellitus.

Type 2 diabetes mellitus it is long term metabolic disorder that is characterized by high blood sugar insulin resistance, and relative lack of insulin common symptoms include increased thirst, frequent urination, and unexplained wt loss symptoms may also include increased hunger, feeling tired and sore that do not heal. Type 2 diabetes primarily occurs as a result of obesity and not enough exercise some people are more genetically at risk than other type 2 diabetes makes up about 90% of cases of diabetes, with the other 10% due

primarily to diabetes mellitus type 1 and there is an absolute lack of insulin due to breakdown islet cells in the pancreas, diagnosis of diabetes is by blood tests such as fasting plasma, glucose, oral glucose tolerance tests.

The medication metformin is typically recommended many people may eventually also require insulin injection. Those on insulin routinely checking blood sugar levels is advised, however this may not be needed in those taking pills. SGLT2 inhibitors is novel class used in the treatment of Diabetes Mellitus 2.

Novel drugs used in type 2 Diabetes mellitus

SGLT-2 inhibitors

MO: Inhibits renal glucose reabsorption and increases urinary glucose excretion

Protective effects on b-cell function and/or mass – Yes (preclinical and clinical trials)

Risk for hypoglycemia- Neutral

Weight Loss (up to 4.7 kg)

Common Side effect or Warnings: Genital infection

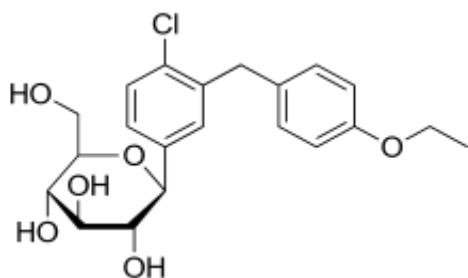
Potential for serious urinary tract infection.

Polyuria, volume depletion,

Hypotension, and dizziness

Increased LDL-C and transient increase in creatinine

Drug name: Dapagliflozin
Structure



IUPAC name: (2S,3R,4R,5S,6R)-2-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol

CAS No: 461432-26.8

Molecular Formula: C₂₁H₂₅ClO₆

Molecular Weight: 408.875 g/mol

Mechanism of action

A competitive inhibitor of the sodium glucose transport subtype 2 protein, dapagliflozin blocks glucose reabsorption into the kidney, resulting in the elimination of blood glucose through the urine

Drug development

Dapagliflozin was the first approved SGLT2 inhibitor, and there is much published clinical trial data. In 24-week, placebo-controlled, phase 3 trials, dapagliflozin (2.5, 5 and 10 mg once daily) used as monotherapy or as add-on therapy to metformin, glimepiride, pioglitazone or insulin reduced HbA1c and fasting plasma glucose in patients with type 2 diabetes. A long term follow-up trial also showed beneficial effects of dapagliflozin. Dapagliflozin added to metformin for 102 weeks resulted in sustained reductions in HbA1c, fasting blood glucose and weight without increased risk of hypoglycemia in patients with type 2 diabetes inadequately controlled by metformin alone. At week 102, mean changes from baseline HbA1c (8.06%) were +0.02% for placebo compared with -0.48% (P = 0.0008), -0.58% (P < 0.0001) and -0.78% (P < 0.0001) for dapagliflozin 2.5–5 and 10mg, respectively. In addition, all dapagliflozin groups had sustained reductions from baseline in fasting plasma glucose and bodyweight at 102 weeks, whereas increases were noted in placebo treated patients for both of these outcomes. Dapagliflozin was also compared with glipizide in patients whose hyperglycaemia was inadequately controlled by metformin. After 1 year, a similar HbA1c reduction from baseline of -0.52% was seen with dapagliflozin (≤10 mg/day) and glipizide (≤20 mg/day). A decrease from baseline in bodyweight of -3.2 kg occurred with dapagliflozin, compared with a weight gain of 1.4 kg with glipizide. Dapagliflozin has the longest term follow-up results among SGLT2 inhibitors. In a randomized, double-blind trial of dapagliflozin (≤10 mg/day) vs glipizide (≤20 mg/day) as add-on to metformin in type 2 diabetes, dapagliflozin was non-inferior to glipizide in HbA1c change at 52 weeks (both-

0.52%), and produced weight loss. The 4-year data showed that the effect of therapy on HbA1c was attenuated over time in both groups, but dapagliflozin showed more persistent benefits vs glipizide (change from baseline of -0.1 vs +0.2%): treatment difference -0.30% (95% confidence interval (CI) -0.51 to -0.09; Table 4). Sustained and stable weight loss was observed with dapagliflozin vs weight gain with glipizide (-3.95 vs +1.12 kg): treatment difference -5.07 kg (95% CI -6.21 to -3.93). Mean systolic blood pressure was reduced with dapagliflozin, but not with glipizide (difference: -3.7 mmHg, 95% CI -5.9 to -1.4).

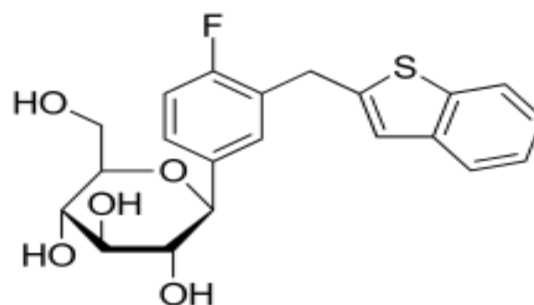
ADR: Symptoms of high blood sugar (hyperglycemia) include thirst, increased urination, confusion, drowsiness, flushing, rapid breathing, and fruit breath odor.

Dose: initially 5 mg and increase upto 10 mg per day.

Brand name: Foxiga Tablet (Bristol-Mayers k.k).

Drug name: Ipragliflozin

Structure



IUPAC name

(2S,3R,4R,5S,6R)-2-[3-1-(benzothien-2-ylmethyl)-4-fluorophenyl]-6-(hydroxymethyl)oxane-3,4,5-triol.

CAS no: 761423-87-4.

Molecular Formula: C₁₂H₂₁FO₅S.

Molecular weight: 404.452g/mol.

Mechanism of action: Ipragliflozin blocks competitively inhibit SGLT2.

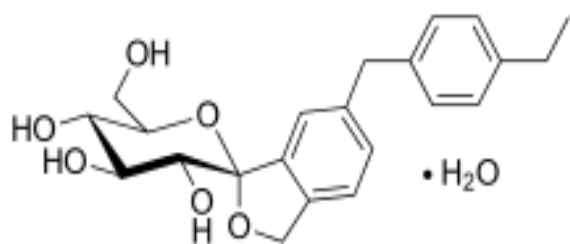
Drug development

In a 24-week trial in patients with type 2 diabetes inadequately controlled with metformin alone, ipragliflozin (50 mg/day) decreased HbA1c by -0.87% vs an increase of 0.38% with placebo (P < 0.001). Bodyweight was also reduced with ipragliflozin (-2.3 kg vs -0.6 kg) 53. The beneficial effects of ipragliflozin (50–100 mg/day) on HbA1c (-0.51%) and bodyweight (-3.41 kg) were sustained for up to 52 weeks in Japanese patients with type 2 diabetes.

ADR: Hypoglycemia, dehydration

Dose: Tablet 25mg and 50 mg

Brand name: Suglat Tablet (Astellas Pharma inc).

Drug name: Luseogliflozin**Structure**

IUPAC name: (2S,3R,4R,5S,6R)-2-[5-(4-ethoxyphenyl)methyl]-2-methoxy-4-methylphenyl]-6-(hydroxymethyl)thiane-3,4,5-triol

CAS no: 898537-18-3

Molecular formula: C₂₃H₃₀O₆S

Molecular Weight: 434.574g/mol

Mechanism of action: Inhibits renal glucose reabsorption and increases urinary glucose excretion

Drug development

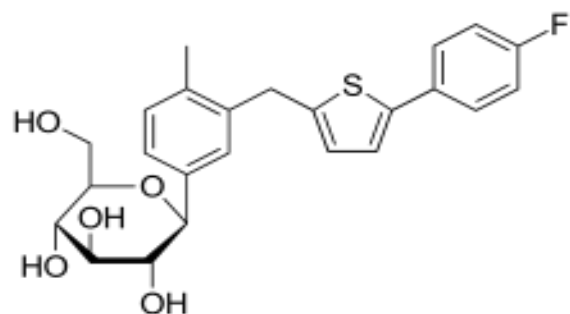
Clinical trials of luseogliflozin as monotherapy or add-on therapy to five types of oral antidiabetic drugs for 52 weeks in Japanese patients with type 2 diabetes mellitus showed that luseogliflozin improves glycemic control and reduces bodyweight. Changes in HbA1c after 52 weeks were monotherapy: -0.50%, add-on to glimepiride: -0.63%, add-on to metformin: -0.61%, add-on to DPP4 inhibitors: -0.52%, add-on to pioglitazone: -0.60%, add-on to glinide: -0.59%, and add-on to a-glucosidase inhibitor: -0.68%. Changes in bodyweight after 52 weeks were monotherapy: -2.7 kg, add-on to glimepiride: -2.2 kg, add-on to metformin: -2.9 kg, add-on to DPP4 inhibitors: -2.0 kg, add-on to pioglitazone: -2.3 kg, add-on to glinide: -2.9 kg and add-on to a-glucosidase inhibitor: -2.8 kg. Furthermore, luseogliflozin decreased blood pressure and showed trends toward improvement in plasma lipids (triglyceride and high-density lipoprotein (HDL) cholesterol) at week 52 compared with baseline.

ADR: Hypoglycemia, Renal impairment, Diabetic Ketoacidosis, Dehydration

Dose: 2.5mg and 5 mg

Brand name: Lusefi Tablet (Taisho Pharma Coorporation)

Drug name: Canagliflozin

Structure

IUPAC name: (2S,3R,4R,5S,6R)-2-[3-[[5-(5-fluorophenyl)thiophin-2-yl]methyl]-4-methylphenyl]-6-(hydroxymethyl)oxane-3,4,5-triol

CAS no: 842133-18-0

Molecular Formula: C₂₄H₂₅FO₅S

Molecular weight: 444.517g/mol

Mechanism of action

Canagliflozin anhydrous is the anhydrous form of canagliflozin, a C-glycoside with thiophene ring that is an orally available inhibitor of sodium glucose transporter 2 (SGLT2) with antihyperglycemic activity. Canagliflozin is also able to reduce body weight and has low risk for hypoglycemia.

Drug development

Out of 1,450 patients who received ≥ 1 dose of double blind study drug (mITT population), 1,161 (80.1%) patients completed the 52 week core period and 1,151 (79.4%) patients entered the 52 week extension period. Canagliflozin is the first SGLT2 inhibitor approved by the US Food and Drug Administration (FDA), and was available on the market in 2013. At week 26 of monotherapy, canagliflozin 100 mg and 300 mg reduced HbA1c vs placebo (-0.77, -1.03, +0.14%, respectively; $P < 0.001$). At week 52, canagliflozin 100 mg and 300 mg showed non inferiority, and canagliflozin 300 mg showed statistical superiority to sitagliptin in lowering

HbA1c (-0.73, -0.88, -0.73%, respectively). Canagliflozin 100 and 300 mg reduced bodyweight vs placebo (week 26: -3.7, -4.2, -1.2%, respectively; $P < 0.001$) and sitagliptin (week 52: -3.8, -4.2, -1.3%, respectively; $P < 0.001$). Both canagliflozin doses reduced fasting blood glucose and systolic blood pressure vs placebo (week 26) and vs sitagliptin (week 52; $P < 0.001$).

In the combination therapy, canagliflozin also improved glycemic control, reduced bodyweight and was generally well tolerated in type 2 diabetes patients on metformin plus sulphonylurea over 52 weeks. HbA1c was significantly reduced with canagliflozin 100 and 300 mg vs placebo at week 26 (-0.85, -1.06, -0.13%; $P < 0.001$); these reductions were maintained at week 52 (-0.74, -0.96, 0.01%). Reductions in HbA1c with canagliflozin 100 mg (-0.82%) and 300 mg/day (-0.93%) were non-inferior to those with glimepiride (titration of glimepiride ranged from a starting dose of 1 mg to a maximum dose of 6 or 8 mg; -0.81%) over the course of 52 week of treatment in patients on background metformin. Canagliflozin 300 mg/day was superior to glimepiride in reducing HbA1c, and both doses of canagliflozin were superior to glimepiride

In reducing bodyweight (-3.7 kg with 100 mg/day, -4.0 kg with 300 mg/day vs +0.7 kg with glimepiride). In the body composition sub study, patients had baseline characteristics and weight changes over 52 weeks that were generally similar to those reported in the main

study. In the canagliflozin groups, roughly two-thirds of the reduction in bodyweight was from fat mass, and one-third was from lean body mass; the increase in bodyweight with glimepiride included both fat and lean body mass. Analysis of abdominal fat in the canagliflozin groups with computed tomography imaging showed a slightly greater reduction in visceral adipose tissue than that in subcutaneous adipose tissue. In the follow-up study of the aforementioned study up to 2 years, HbA1c reductions were maintained with canagliflozin 100 and 300 mg, and glimepiride placebo at week 104 (-0.65, -0.746 and -0.55%), and both doses of canagliflozin were superior to glimepiride in reducing bodyweight (-4.1% with 100 mg/day, -4.2% with 300 mg/day vs +0.9% with glimepiride).

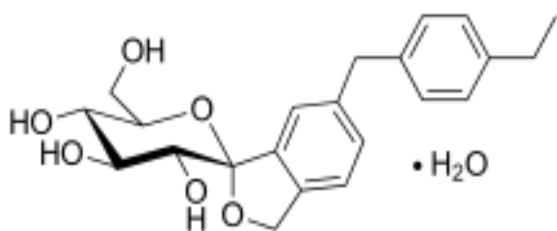
ADR: Renal impairment, hypoglycemia, Dehydration
Diabetic Ketoacidosis, Hypersmolar Hyperglycemic syndrome

Dose: 100mg

Brand name: Invokana

Drug name: Tofogliflozin

Structure:



IUPAC name: (3S,3'R,4'5,6'R)-5-[(4-ethylphenyl)methyl]-66'-(hydroxymethyl)spiro[1H-2-benzofuran-3,2'-oxane]-3',4',5',5'-triol

CAS no: 903565-83-3

Molecular Formula: C₂₂H₂₆O₆·H₂O

Molecular Weight: 404.45

Mechanism of action

An inhibitor of SGLT2 tofogliflozin selectively inhibited in kidneys, which resulted in decrease of renal glucose reabsorption, thereby increasing urinary glucose excretion and lowering plasma glucose, in type 2 Diabetes patients

Drug development

Clinical trials of tofogliflozin as monotherapy or add-on therapy to oral antidiabetic drugs for 52 weeks in Japanese patients with type 2 diabetes mellitus showed that tofogliflozin improved glycemic control and reduced bodyweight. With monotherapy, change in HbA1c from baseline was -0.7% (both 20 and 40 mg), and change in bodyweight was -3.1 kg (20 mg) and -3.4 kg (40 mg). With combination therapy, change in HbA1c from baseline was -0.8% (20 mg) and -0.9% (40 mg), and change in bodyweight was -2.5 kg (20 mg) and -3.0 kg (40 mg). Furthermore, reduced systolic and diastolic blood pressure, improved homeostasis model assessment of insulin resistance, increased serum adiponectin and HDL cholesterol levels were secondarily observed.

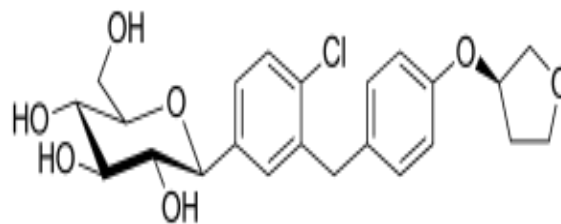
ADR: Dehydration, Hypoglycemia, ketoacidosis

Dose: 20 mg initial

Brand name: Apleway Tablet (Sanofi K.K.)

Drug Name: Empagliflozin

Structure



IUPAC name: (2S,3R,4R,5,6R)-2-[4-chloro-3-[[4-[(3-oxolan-3-yl)oxy]phenyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol.

CAS no: 864070-44-0.

Molecular formula: C₂₃H₂₇ClO₃.

Molecular weight: 450.912 gm/mol.

Mechanism of Action

Empagliflozin is a sodium glucose co-transporter-2 (SGLT-2) inhibitor. SGLT-2 co-transporters are responsible for reabsorption of glucose from the glomerular filtrate in the kidney. The glucuretic effect resulting from SGLT2 inhibition reduces renal threshold for glucose, resulting in increased glucose excretion. Additionally, it contributes to reduced hypoglycemia, assists weight loss, and reduces blood pressure.

Drug development

Empagliflozin (5–25 mg/day for 12 weeks) increased glucose excretion, and decreased fasting plasma glucose (-31.1 mg/dL at 25 mg vs an increase of 0.8 mg/dL with placebo), HbA1c (-0.63% at 25 mg vs an increase of 0.09%) and bodyweight (-2.0 kg at 2 mg vs -0.8 kg) in patients with type 2 diabetes. In a randomized to double-blind empagliflozin (10, 25 mg) or placebo add-on to basal insulin for 78 weeks, empagliflozin significantly reduced HbA1c (empagliflozin 10 mg: -0.48%, empagliflozin 25 mg: -0.64%, placebo: -0.02%), bodyweight (empagliflozin 10 mg: -2.2 kg, empagliflozin 25 mg: -2.0 kg, placebo: +0.7 kg; Table 4). Furthermore, empagliflozin 10 mg significantly reduced systolic blood pressure (empagliflozin 4 mg: -4.1 mmHg, empagliflozin 25 mg: -2.4 mmHg, placebo: +0.1 mmHg). In a randomized, open-label, 78-week blinded study of empagliflozin (monotherapy at doses of 10 mg or 25 mg, and add-on to metformin) with metformin, and sitagliptin as add-on to metformin, changes from baseline in HbA1c at week 90 were -0.34 to -0.63% with empagliflozin, -0.56% with metformin, and -0.40% with sitagliptin. Changes in weight from baseline at week 90 were -2.2 to -4.0 kg with empagliflozin, -1.3 kg with metformin and -0.4 kg with sitagliptin. Thus, long-term empagliflozin treatment can provide sustained glycemic and weight control in patients with type 2 diabetes.

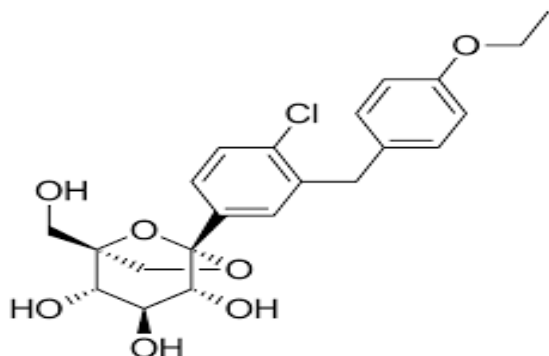
ADR: Renal impairment, Hypoglycemia, dehydration.

Dose: initially 10 mg and 25 mg

Brand name: Jardian

Drug Name: Ertugliflozin

Structure



IUPAC name: (1S,2S,3S,4R,5S)-5-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol

CAS No: 1210344-57-2

Molecular Formula: C₂₂H₂₅ClO₇

Molecular weight: 436.885g/mol.

Mechanism of action

Inhibition of sodium-dependent glucose co transporter 2 (SGLT2), a transporter located in the kidney, is a mechanism that promotes glucosuria and therefore, reduction of plasma glucose concentration. Since the mechanism operates in a glucose-dependent and insulin-independent manner, and is associated with weight loss, it has emerged as a very promising approach to the pathophysiologic treatment of type 2 diabetes. Ertugliflozin (PF-04971729), an anti-diabetic agent currently in development (Phase 3 clinical trials) and belonging to a new class of SGLT2 inhibitors bearing a dioxabicyclo[3.2.1]octane bridged ketal moiety ADR: dehydration, hypoglycemia

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