



NOVEL DRUGS APPROACHES IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus belongs to the most rapidly increasing diseases worldwide. Approximately 90–95% of these patients suffer from type 2 diabetes mellitus. 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. Type 2 diabetes mellitus (DM) is a disorder characterised by insulin resistance and a progressive decline in pancreatic beta-cell function associated with increasing hyperglycaemia. This review will briefly summarize novel type 2 anti-diabetic drugs. Their suitability as ‘ideal anti-diabetic drugs’ will be discussed. 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. The aim of this article is to present an overview of all the available novel type 2 antidiabetic drugs according to the different classes, their mechanisms of action and pharmacological profiles, and to assist physicians to make the correct choice for their patients. This article is written about the need for novel drug delivery systems in the treatment of type 2.

KEYWORDS: Type 2 diabetes mellitus, Qtern, Lixisenatide, Soliqua, Invokamet, Xultophy. long term efficacy. SGLT2 inhibitors.

INTRODUCTION

Diabetes was first documented by the Egyptians and is characterised by weight loss and polyuria. However, it was the Greek physician Aetaeus who coined the term diabetes mellitus (DM). In Greek, diabetes means “to pass through” and mellitus is the Latin word for honey (referring to sweetness).^[1] Diabetes mellitus (DM) is one of the most challenging and burdensome chronic diseases of the 21st century. It is a group of metabolic disorders characterized by a chronic hyperglycemic condition resulting from insufficient action of insulin.^[2]

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 types, 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.

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 weight loss symptoms may also include increased hunger, feeling tired and sore that do not heal.

1. INVOKAMET (Canagliflozin/Metformin)

On August 8, 2014, the combination of canagliflozin (Invokana) plus metformin hydrochloride (Invokamet; Janssen Pharmaceuticals) in a single tablet was approved by the US Food and Drug Administration (FDA) for the treatment of patients with type 2 diabetes mellitus.^[3]

Mechanism of Action

Canagliflozin plus metformin combines 2 oral antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus—canagliflozin, an SGLT2 inhibitor, and metformin, a member of the biguanide class. SGLT2, expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion. Metformin is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes by lowering basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves

insulin sensitivity by increasing peripheral glucose uptake and utilization.^[4]

Dosage And Administration

The dosing of canagliflozin plus metformin is individualized based on the patient's current antidiabetes drug regimen. The combination of canagliflozin plus metformin is taken twice daily with meals, with gradual dose escalation to reduce metformin-related gastrointestinal side effects. The daily dose of metformin should not exceed 2000 mg, and the daily dose of canagliflozin should not exceed 300 mg in patients with an estimated glomerular filtration rate (eGFR) of ≥ 60 mL/min/1.73 m².^[4]

Contraindication

The combination of canagliflozin plus metformin is contraindicated in patients with renal impairment (eg, serum creatinine levels ≥ 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR < 45 mL/min/1.73m²), which may also result from conditions such as cardiovascular collapse, acute myocardial infarction, or septicemia; endstage renal disease; or patients on dialysis. Canagliflozin plus metformin is also contraindicated in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, or in patients with a history of a hypersensitivity reaction to canagliflozin or to metformin.^[4]

Safety

The most common adverse reactions ($\geq 5\%$) associated with the use of canagliflozin are female genital mycotic infections, urinary tract infection, and increased urination. The most common adverse reactions ($\geq 5\%$) associated with the use of metformin are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.^[4]

2. SYNJARDY XR (Empagliflozin/Metformin)

SYNJARDY XR (empagliflozin and metformin hydrochloride extended-release) tablets, for oral use Approved August 2015.

Mechanism of Action

Synjardy is a combination of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor and metformin, a biguanide. Empagliflozin: Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Metformin hydrochloride: Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. It is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents.

Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike SUs, metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.^[5]

Dosage Administration

In patients on metformin, switch to SYNJARDY containing empagliflozin 5mg with a similar total daily dose of metformin; In patients on empagliflozin, switch to SYNJARDY containing metformin 500mg with a similar total daily dose of empagliflozin; In patients already treated with empagliflozin and metformin, switch to SYNJARDY containing the same total daily doses of each component. Take SYNJARDY twice daily with meals; with gradual dose escalation to reduce the gastrointestinal side effects due to metformin. In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating SYNJARDY. Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin 2000mg and empagliflozin 25mg.^[7]

Contraindication

Moderate to severe renal impairment (eGFR below 45mL/min/1.73m), end stage renal disease, or dialysis. Metabolic acidosis, including diabetic ketoacidosis. History of serious hypersensitivity reaction to empagliflozin or metformin.^[6]

Pharmacokinetics

The results of a bioequivalence study in healthy subjects demonstrated that SYNJARDY (empagliflozin/metformin hydrochloride) 5mg/500mg, 5mg/1000mg, 12.5mg/500mg, and 12.5mg/1000mg combination tablets are bioequivalent to co-administration of corresponding doses of empagliflozin and metformin as individual tablets.

Administration of 12.5mg empagliflozin/1000mg metformin under fed conditions resulted in a 9% decrease in AUC and a 28% decrease in C_{max} for empagliflozin, when compared to fasted conditions. For metformin, AUC decreased by 12% and C_{max} decreased by 26% compared to fasting conditions. The observed effect of food on empagliflozin and metformin is not considered to be clinically relevant.^[7]

Adverse Reaction

Most common adverse reactions associated with empagliflozin (5% or greater incidence) were urinary tract infection and female genital mycotic infections. Most common adverse reactions associated with metformin ($>5\%$) are diarrhea, nausea/vomiting,

flatulence, abdominal discomfort, indigestion, asthenia, and headache.^[5]

3. QTERN (dapagliflozin /saxagliptin)

Approved February 2017

Qtern combines two antihyperglycemic agents: dapagliflozin, a sodium-glucose cotransporter 2 (SGLT-2) inhibitor, and saxagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor.

Mechanism of Action

Qtern combines saxagliptin and dapagliflozin with complementary mechanisms of action to improve glycaemic control. Saxagliptin, through the selective inhibition of dipeptidyl peptidase-4 (DPP-4), enhances glucose-mediated insulin secretion (incretin effect). Dapagliflozin, a selective inhibitor of sodium-glucose co-transporter 2 (SGLT2), inhibits renal glucose reabsorption independently of insulin. Actions of both medicinal products are regulated by the plasma glucose.^[8]

Side Effect

Upper respiratory tract infection, urinary tract infection, Dyslipidemia.^[9]

Dosage And Administration

Qtern is taken orally once daily. It may be taken at any time of day with or without food.

Tablet is to be swallowed whole. If a dose is missed and it is ≥ 12 hours until the next dose, the dose should be taken. If a dose is missed and it is < 12 hours until the next dose, the missed dose should be skipped and the next dose taken at the usual time.^[8]

Contraindication

Hypersensitivity to the active substances or the excipients or history of a serious hypersensitivity reaction, including anaphylactic reaction, anaphylactic shock, and angioedema, to any dipeptidyl peptidase-4 (DPP-4) inhibitor or to any sodium-glucose co-transporter 2 (SGLT2) inhibitor^[8]

Safety

The safety profile of the saxagliptin/dapagliflozin combination in these clinical studies for up to 52 weeks was comparable to those of the individual components^[9]

4. SOLIQUA (insulin glargine/ Lixisenatide)

SOLIQUA™ 100/33 (insulin glargine and lixisenatide injection), for subcutaneous use Initial U.S. Approval: 2016.

Mechanism of Action

SOLIQUA 100/33 is a combination of insulin glargine, abasal insulin analog, and lixisenatide, a GLP-1 receptor agonist. Insulin glargine: The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose

by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis. Lixisenatide: Lixisenatide is a GLP-1 receptor agonist that increases glucose-dependent insulin release, decreases glucagon secretion, and slows gastric emptying.^[11]

Dosage And Administration

Discontinue therapy with lixisenatide or basal insulin prior to initiation of SOLIQUA 100/33. In patients inadequately controlled on less than 30 units of basal insulin or on lixisenatide, the starting dosage is 15 units given subcutaneously once daily. Inject once a day within the hour prior to the first meal of the day. Maximum daily dosage is 60 units (60 units of insulin glargine and 20 mcg of lixisenatide). SOLIQUA 100/33 Pen delivers doses from 15 to 60 units with each injection. Use alternative antidiabetic products if patients require a SOLIQUA 100/33 daily dosage below 15 units or over 60 units See Full Prescribing Information for titration recommendations. Inject subcutaneously in thigh, upper arm, or abdomen. Do not administer intravenously, intramuscularly, or by an infusion pump. Do not dilute or mix with any other insulin products or solutions.^[11]

Contraindication

During episodes of hypoglycemia Hypersensitivity to SOLIQUA 100/33 either of the active drug substances (insulin glargine or lixisenatide), or any of its excipients. Hypersensitivity reactions including anaphylaxis have occurred with both lixisenatide and insulin glargine.^[11]

Adverse Reaction

Anaphylaxis and Serious Hypersensitivity Reactions, Pancreatitis, Hypoglycemia, Acute Kidney Injury, Hypokalemia.^[11]

5. GLYXAMBI [linagliptin/ empagliflozin]

A Novel Fixed-Dose Combination Agent for Type 2 Diabetes On February 2, 2015, the US Food and Drug Administration (FDA) approved empagliflozin plus linagliptin (Glyxambi; BoehringerIngelheim/Eli Lilly) tablets as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes when treatment with empagliflozin and linagliptin is appropriate. This fixed-dose combination contains 10 mg or 25 mg of empagliflozin and 5 mg of linagliptin, combining the properties of an SGLT2 and a DPP-4 in a single tablet.^[11]

Mechanism of Action

Empagliflozin plus linagliptin therapy combines 2 medications with complementary mechanisms of action; empagliflozin is an SGLT2 inhibitor, and linagliptin is a DPP-4 inhibitor. SGLT2 is a protein that facilitates the reabsorption of glucose from the kidney into the blood. By inhibiting SGLT2, empagliflozin lowers blood glucose levels and increases glucose excretion. DPP-4 is

an enzyme that cleaves GLP-1 and glucose-dependent insulinotropic polypeptide, 2 intestinal hormones that regulate the postprandial production of insulin and glucagon by the pancreas. As an inhibitor of DPP-4, linagliptin increases the concentrations of these incretin hormones, which stimulates the release of insulin in a glucose-dependent manner and decreases glucagon levels in the blood. GLP-1 also reduces glucagon secretion from the pancreas, which results in lowered glucose production by the liver.^[12]

Dosage And Administration

Empagliflozin plus linagliptin fixed-dose combination should be started at 10mg empagliflozin/5mg linagliptin, taken once daily in the morning, with or without food.

The higher dose of empagliflozin plus linagliptin (25mg empagliflozin/5mg linagliptin) once daily may be considered if the initial dose is well-tolerated.^[12]

Safety

The safety of empagliflozin plus linagliptin (empagliflozin 10 or 25mg/linagliptin 5mg) was evaluated in 1363 patients with type 2 diabetes who received treatment for a maximum of 52 weeks in active-controlled clinical trials. Based on pooled analyses of these studies, the most common adverse reactions associated with empagliflozin plus linagliptin therapy included urinary tract infection (a predefined adverse event grouping that also includes asymptomatic bacteriuria and cystitis), nasopharyngitis, and upper respiratory tract infection.^[12]

6. XULTOPHY (Insulin degludec/Liraglutide)

XULTOPHY® 100/3.6 (insulin degludec and liraglutide injection), for subcutaneous use Initial U.S. Approval: 2016.

Mechanism of Action

Insulin degludec The primary activity of insulin degludec is the regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis and proteolysis, and enhances protein synthesis. **Liraglutide** Liraglutide is a Glucagon-Like Peptide-1 (GLP-1) receptor agonist that increases glucose-dependent insulin release, decreases glucagon secretion, and slows gastric emptying.^[8]

Pharmacokinetics

Absorption In patients with type 2 diabetes (mean body weight 87.5kg) reaching the maximum daily dose (50 units/1.8mg) of XULTOPHY® 100/3.6, the estimated mean steady-state exposure (AUC 0-24 h) of insulin degludec was 113h*nmol/L and of liraglutide 1227h*ng/mL based on population pharmacokinetic analysis. The corresponding maximum concentrations were 5196 pmol/L for insulin degludec and 55ng/mL for liraglutide. Steady state concentrations of insulin

degludec and liraglutide are reached after 2-3 days of daily administration. Distribution Insulin degludec and liraglutide are extensively bound to plasma proteins >99% and >98%, respectively. Metabolism Insulin degludec Degradation of insulin degludec is similar to that of human insulin; all metabolites formed are inactive. Liraglutide During the initial 24 hours following administration of a single [3H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination. Elimination. The half-life of insulin degludec is approximately 25 hours and the half-life of liraglutide is approximately 13 hours.^[8]

Dosage And Administration

Discontinue therapy with liraglutide or basal insulin prior to initiation of XULTOPHY® 100/3.6 Recommended starting dosage is 16 units given subcutaneously once daily. Administer once daily at same time each day with or without food. Maximum daily dosage is 50 units doses from 10 to 50 units with each injection; each XULTOPHY® 100/3.6 dosage unit contains 1 unit of insulin degludec and 0.036mg of liraglutide. Use alternative antidiabetic products if patients require a XULTOPHY® 100/3.6 daily dosage: Persistently below 16 units, or o Over 50 units. See Full Prescribing Information for titration recommendations. Inject subcutaneously in thigh, upper arm or abdomen. Do not administer intravenously, intramuscularly, or by an infusion pump. Do not dilute or mix with any other insulin products or solutions.^[8]

Contraindication

In patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) [see Warnings and Precautions. During episodes of hypoglycemia. In patients with hypersensitivity to XULTOPHY® 100/3.6, either of the active drug substances (insulin degludec or liraglutide), or any of its excipients.^[8]

7. TANZEUM

On April 15, 2014, the US Food and Drug Administration (FDA) approved albiglutide (Tanzeum; GlaxoSmithKline), a GLP-1 receptor agonist subcutaneous injection, as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus.^[13]

Mechanism of Action

Albiglutide is an agonist of the GLP-1 receptor that augments glucose-dependent insulin secretion. In addition, albiglutide slows gastric emptying.^[14]

Dosage and Administration

Albiglutide is administered once weekly at any time of the day, with or without food, via subcutaneous injection

(ie, injection pen) in the abdomen, thigh, or upper arm; the initial dose is 30 mg. The dose can be increased to 50 mg once weekly in patients who require additional glycemic control. If a dose of albiglutide is missed, it should be administered within 3 days of the missed dose. The lyophilized powder that is contained in the injection pen must be reconstituted before administration.^[14]

Adverse Effect

The most common adverse reactions reported in $\geq 10\%$ of patients who received albiglutide and were more common than in patients who received placebo included upper respiratory tract infection, diarrhea, nausea, and injection-site reaction.

This new drug therapy provides patients a treatment option with a longer duration of action, which may offer patients the added convenience of fewer dosing versus treatment regimens with more frequent dosing.^[13,14]

8. Luseogliflozin

Brand name: Lusefi Tablet (Taisho Pharma Coorporation)

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

ADR: Hypoglycemia, Renal impairment, Diabetic Ketoacidosis, Dehydration.

Dose: 2.5mg and 5mg.

9. AFREZZA [insulin human inhalation powder]

FDA Approves On June 27, 2014, the US Food and Drug Administration (FDA) approved insulin human inhalation powder (Afrezza; MannKind Corporation), a rapid-acting inhaled insulin that is used to improve glycemic control in adults with diabetes.^[15]

It is used in treatment of both type 1 and type 2 diabetes.

Mechanism of Ation

The new medication is a rapid-acting inhaled insulin. Insulin lowers HbA1c levels by stimulating peripheral glucose uptake via skeletal muscle and fat and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in adipocytes, inhibits proteolysis, and enhances protein synthesis. The insulin contained in this new inhalation powder is regular human insulin. After pulmonary absorption into systemic circulation, the metabolism and elimination of this new insulin powder are comparable with regular human insulin. The peak insulin levels were achieved within 12 to 15 minutes

after administration of insulin human inhalation powder, with serum insulin concentrations declining to baseline levels by approximately 180 minutes.^[16]

Dosage and Administration

Before patients begin treatment with Afrezza, clinicians must perform a thorough medical history, physical examination, and spirometry testing (FEV1) to rule out the presence of chronic lung diseases, such as asthma or COPD. Afrezza is administered to adults (18 years of age or older) at the beginning of a meal using a single inhalation per cartridge. Initial dosing recommendations are as follows:

In insulin-naïve patients, initiate 4 units of TI at each meal. In patients receiving SC prandial insulin, use the dose conversion to determine the appropriate TI dose at each meal. In patients receiving SC premixed insulin, determine the total daily dose of premixed insulin and divide half of this dose equally into three meals a day. The estimated SC mealtime dose should then be converted to an appropriate TI dose. The remaining half of the total daily insulin dose should be given as a basal insulin dose. Subsequent TI doses are adjusted according to the patient's overall glycemic control, metabolic requirements, and blood-glucose monitoring results. Glycemic control should be monitored closely in patients requiring high doses of Afrezza. SC prandial insulin should be considered in patients who require high doses of TI and are not achieving adequate glycemic control.^[17]

Type 2 Diabetes

A 24-week, double-blind, placebo-controlled study was conducted in 479 adults with type 2 diabetes whose disease was inadequately controlled with maximally tolerated doses of metformin only or with ≥ 2 oral antidiabetes agents.

After a 6-week run-in period, 353 patients were randomized to receive either insulin human inhalation powder or an inhaled placebo powder without insulin.

For the first 12 weeks, the insulin doses were titrated and were kept stable for the last 12 weeks of the study.

The doses of oral antidiabetes agents were kept stable.

At week 24, treatment with insulin human plus oral antidiabetes agents provided a significantly greater mean reduction in HbA1c levels compared with placebo.^[16]

Safety

The most common adverse reactions ($\geq 2\%$) associated with insulin human inhalation powder include hypoglycemia, cough, and throat pain or irritation.^[13]

Contraindication

The use of insulin human inhalation powder is contraindicated during episodes of hypoglycemia.

It is also contraindicated in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD).

In addition, insulin human inhalation powder is contraindicated in patients with hypersensitivity to regular human insulin or any of the insulin human inhalation powder excipients.^[16,13]

10. CANAGLIFLOZIN

Brand name: Invokana

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

CAS no: 842133-18-0.

Molecular Formula: (C₂₄H₂₅FO₅S)₂ H₂O.

Molecular weight: 444.517g/mol.

Mechanism of Action

Canagliflozin acts by inhibiting the SGLT2 which accounts for more than 90% of renal glucose reabsorption. Hence the efficacy of this drug also is dependent upon the amount of glucose which is filtered through the glomeruli and enters the tubular lumen and therefore shows maximal effect in patients with uncontrolled T2DM.^[8] Apart from bringing down the blood glucose levels, it has many other beneficial actions like reduction of the glycosylated haemoglobin levels due to the better control of blood glucose levels. It additionally improved the sensitivity of liver to insulin by reducing the blood glucose levels thereby reducing the glucose production from liver. This reduces the general glucotoxic state of the body in patients with T2DM and helps. Since the calories are lost from the body in the form of glucose in urine of the patients taking this drug, it causes a negative energy balance and loss of weight, which is again beneficial in patients of T2DM. This drug also helps in reduction of blood pressure owing to the mild weight loss and diuretic action caused by it. It has a positive effect on blood lipids as well due to mild weight loss caused by it.^[18,19]

Pharmacokinetics

It is given orally and reaches the peak concentration in plasma in about 1-2 hours. The steady state of plasma concentration is achieved in around 4-5 days. Oral bioavailability of canagliflozin is approximately 65%. It has a high plasma protein binding (99%) and it binds mainly to albumin. Food does not interfere with its absorption. It has a half life of 11 hours with a 100 mg dose and of 13hrs with a dose of 300 mg and is mainly metabolised via glucuronidation.^[20] A small part (~7%) of absorbed drug also undergoes oxidation through CYP3A4 enzyme.^[21]

Efficacy Studies

Canagliflozin has been extensively studied both in preclinical and clinical trials and its efficacy as a hypoglycaemic agent has been proved.^[21]

Safety And Tolaribity

The most common side effects associated with canagliflozin are mycotic genital infections, more so in females, urinary tract infections, increased urination, especially at night. Though these infections are easily treatable, they do impair to certain extent, the quality of life of the person receiving treatment. Since canagliflozin is associated with polyuria, effects related to intravascular volume depletion like postural hypotension, increased thirst and a small rise in haematocrit etc. may occur. There is a study going on (CANVAS study) to assess the full and long term effects of canagliflozin on cardiovascular outcomes. It can also cause constipation, rash and allergy in some patients. It can also moderately increase the blood urea nitrogen (BUN), mildly increase serum creatinine and decrease serum urate levels.^[21]

Dosage Regimen And Precaution

It has to be given orally, once daily, before taking the first meal of the day.

According to the recommendations, the starting dose of canagliflozin is 100mg/day.

It can be increased to 300mg/day as per the requirement.^[21]

11. Tofogliflozin

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

IUPAC name

(3S,3'R,4'5,6'R)-5-[(4-ethylphenyl)methyl]-66'(hydroxymethyl)spiro[1H-2-benzfuran-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.

ADR: Dehydration, Hypoglycemia, ketoacidosis.

Dose: 20 mg initial.

12. TRULICITY (dulaglutide)

Mechanism of Action

The primary mechanism of action of dulaglutide, as an incretin mimetic hormone or an analogue of human glucagonlike peptide-1, is to increase insulin secretion when glucose levels are elevated, decrease glucagon secretion, and delay gastric emptying in an effort to lower postprandial glucose level.⁽¹⁹⁾ Dulaglutide also activates the membrane-bound cell surface receptor in pancreatic beta cells known as the GLP-1 receptor.^[22]

Indication and Usage

Dulaglutide is indicated to improve glycemic control in adults with type-2 diabetes mellitus as an adjunct to diet and exercise.^[22]

Pharmacokinetics

The pharmacokinetics of dulaglutide can be seen following subcutaneous administration. The time to maximum concentration at steady state ranges from 24 to 72 hours, with a median of 48 hours. The mean absolute bioavailability of single 0.75-mg and 1.5-mg doses of dulaglutide was 65% and 47%, respectively. Mean volumes of distribution were approximately 19.2 L and 17.4 L, respectively. It is assumed that dulaglutide is degraded into its component amino acids upon administration. However, at steady state, the mean apparent clearance is approximately 0.111 L per hour for the 0.75-mg dose and 0.107 L per hour for the 1.5-mg dose. The elimination half-life of dulaglutide for both doses is approximately five days. Nevertheless, dulaglutide does not require dose adjustments.^[23]

Adverse Effect

The most common side effect of Nausea, Diarrhea, Vomiting, Abdominal pain, Decreased Appetite, Dyspepsia, Fatigue.

At baseline, 2.5% of the population reported retinopathy, and baseline estimated renal function was normal or mildly impaired (estimated glomerular filtration rate 60 mL/min/1.73 m² or higher) in 96% of the pooled study populations.^[23]

Dosage and Administration

Dulaglutide should be administered once weekly at any time of the day. It is to be injected subcutaneously in the abdomen, thigh, or upper arm. The starting dose is 0.75 mg subcutaneously once weekly. The dose can be increased to 1.5 mg once weekly for additional glycemic control. If a dose is missed, administer it within three days (72 hours) of the missed dose.^[24]

Contraindication

Dulaglutide has an absolute contraindication in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.

Dulaglutide should also not be used if there is a history of serious hypersensitivity to dulaglutide or any product components.^[22,23]

13. DAPAGLIFLOZIN

Brand name – Forxiga (Bristol-Mayers k.k).

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

This drug produces a selective and reversible inhibition of the human sodium-glucose cotransporter 2 (SGLT2), reducing glucose renal absorption and thus incrementing its excretion. By inhibiting SGLT2, FARXIGA® (dapagliflozin), a glucuretic, removes glucose and associated calories.^[25]

Pharmacokinetics

It is rapidly absorbed after oral ingestion and reaches its peak plasma concentrations after 2 hours. The absolute oral bioavailability is 78%. Less than 2% is eliminated unaltered, and the rest is metabolized in the liver and kidney, producing an inactive metabolite that is eliminated mainly through renal excretion.^[25]

DOSE

Starting dose 5mg.

In monotherapy or combination therapy use 10mg daily.

It can be taken at any time of the day, with or without food. The tablets should be swallowed entirely.^[25]

CONTRINDICATION

Prior serious hypersensitivity reaction to FARXIGA.

Severe renal impairment (eGFR < 30 mL/min/1.73 m²), end-stage renal disease, or patients on dialysis.^[25]

ADVERSE REACTION

Very frequent: Hypoglycaemia (when added to sulphonylurea or insulin). Frequent (1/100 to <1/10): Vulvovaginitis, balanitis and genital infections, urinary tract infections, back pain, dysuria, polyuria, dyslipidaemia, increase in hematocrit.

Less frequent (1/1,000 to <1/100): Vulvovaginal pruritus, volume depletion, thirst, constipation, hyperhidrosis, nicturia, increase in blood creatinine levels, increase in blood urea. 1,2 The incidence of adverse effects with dapagliflozin in monotherapy was 22% compared to 15% under metformin.^[25]

CONCLUSION

The management of diabetes remains a challenge that requires a variety of risk-reduction strategies and different treatment options. The recent FDA approval of novel type 2 anti-diabetic drugs has made available a new treatment option for the treatment of adults with type 2 diabetes, or combination of novel drugs which improve glycemic control consistently.

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