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"Review On Combination Of Dapagliflozin With Other Oral Antidiabetic Drugs"

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ABSTRACT

Type 2 diabetes mellitus is a prevalent, progressive disease that needs for innovative therapeutic agents to continue an advanced disease management. Sodium-glucose co-transporter 1 (SGLT1) and SGLT2 are responsible for the transport of glucose across the proximal convoluted tubular cells. SGLT2 inhibitors affect glucose levels which gradually reduces glucose levels through the increased glucose filtration and excretion of glucose.

In addition of dapagliflozin to other antidiabetic drugs provides a new therapeutic option for the treatment of type 2 diabetes in patients who have inadequate glycaemic control with other antidiabetic drugs alone. combination therapy provides advantages beyond better glycemic improvement such as reduced incidence of hypoglycemia and cardiovascular events.

Fixed-dose combination of Dapagliflozin plus Metformin are Xigduo XR (dapagliflozin/metformin hydrochloride extended-release), OXRAMET XR, GLEDEPA MET XR. and Saxagliptin and dapagliflozin fixed-dose combination tablets (QternÒ) are indicated in the European Union for the improvement of glycaemic control in adults with type 2 diabetes mellitus (T2DM).

the combination therapy results in a greater improvement in glycemic control and body weight reduction but no difference in blood pressure.

Keywords: Dapagliflozin, Type-2 diabetes, SGLT-2 inhibitor

1. INTRODUCTION

The most prevalent type of diabetes is type 2 diabetes, which develops when blood glucose, commonly known as blood sugar, is too high. The main source of energy is blood glucose, which is derived primarily from the food you eat. Insulin, it is a hormone produced by the pancreas, aids glucose absorption into cells for energy production.

90–95 percent of all diabetes cases are type 2 diabetes, also known as "adult-onset diabetes" or "noninsulin-dependent diabetes." This category includes people who have relative (rather than absolute) insulin insufficiency and peripheral insulin resistance. At first, and typically throughout their lives, these people may not require insulin prescription to survive.(Of and Carediabetes, 2017)

Blood tests that monitor plasma glucose levels can detect Type-2 Diabetes mellitus early. The most frequent diabetes test is fasting blood glucose: a recurring clinically confirmed result of (126 mg/dL) or (7.0 mmol/L) of fasting blood glucose can diagnosis diabetes. Fasting for at least the previous 8 hours is required for this test, and blood must be obtained in the morning. A 2-hour PG of (200 mg/dL) or (11.1 mmol/L) for patients who have complained of diabetes symptoms such as polydipsia, polyuria, or weight loss is another test for diabetes. After a glucose load of 75 g, a positive result of a 2-hour oral glucose tolerance test will be a PG level of (200 mg/dL) or (11.1 mmol/L) after a glucose load which contain 75 g of glucose solution in water. (Sciences, 2021)

Table 1: **Oral anti diabetic agents**

SR No.	Class	Example	Mechanism of action	Uses (Applications)
1	Biguanides	Metformin	Decrease HGP, Increase Glucose Uptake in Muscle.	First line drug for type 2 diabetes mellitus.
2	Sulfonylureas	Glimepiride, Glibenclamide, Glipizide.	Increase Insulin secretion.	Combination partner of Metformin.
3	DPP-4 Inhibitor	Alogliptin, Linagliptin, Sitagliptin, Saxagliptin.	-Increase Glucose-Dependent insulin secretion. -Decrease Glucagon Secretion.	Insufficient Glycemic control with Metformin, alone raise risk of Hypoglycemia.
4	GLP-1 receptor agonist	Albiglutide, Duaglutide, Exenatide, Exenatide XR, Liraglutide.	-Increase Glucose-Dependent insulin secretion. -Decrease Glucagon Secretion.	Insufficient Glycemic control with Metformin, alone raise risk of Hypoglycemia.
5	Alpha-glucosidase Inhibitor	Acarbose	Delay Carbohydrate absorption from intestine.	Used in type 2 diabetes mellitus.
6	SGLT-2 inhibitor	Canagliflozin, Dapagliflozin, Empagliflozin.	Increase urinary excreation of Glucose.	Used in type 2 diabetes mellitus, alone or in the combination with other antidiabetic drugs.
7	Thiazolidinediones	Rosiglitazone, Pioglitazone.	Increase Glucose uptake in muscle and fat.	Used in combination with other antidiabetic drugs.
8	Glinides	Nateglinide, Repaglinide.	Increase Insulin secretion.	Superior to sulfonylureas and use for patient with renal insufficiency.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors an appealing alternative for early metformin combination therapy. These drugs have an insulin-independent mechanism of action that lowers blood glucose levels by increasing glucose excretion through urine. When compared to a placebo, they also reduce body weight and blood pressure.(Milder *et al.*, 2019)

1.1. ABOUT DAPAGLIFLOZIN

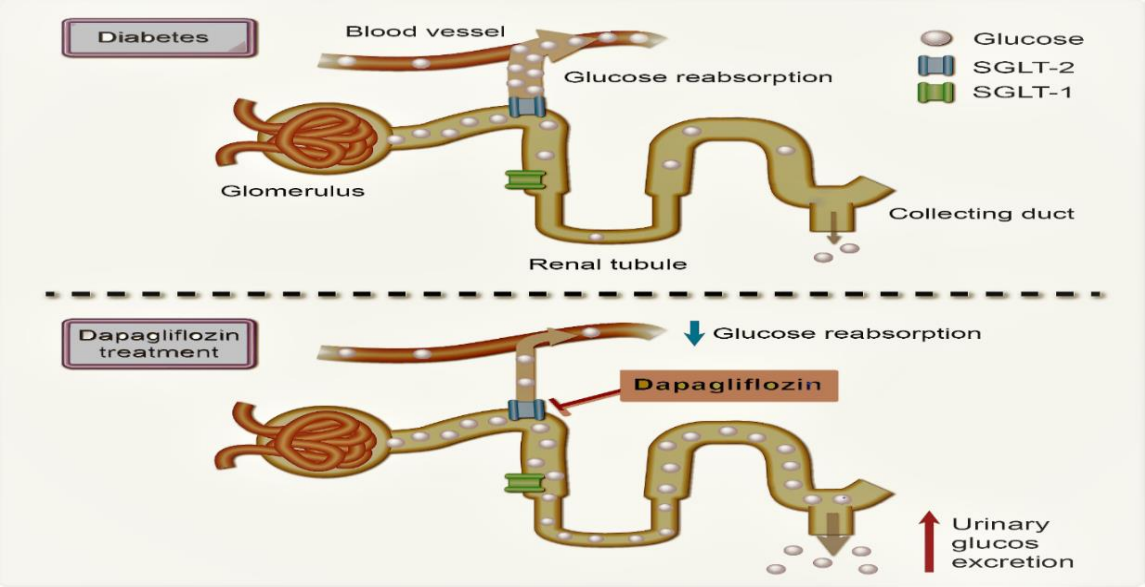
It is the first in a new class of oral selective sodium-glucose cotransporter 2 (SGLT2) inhibitors for treating type 2 diabetes. Dapagliflozin improves hyperglycemia by inhibiting renal glucose reabsorption through sodium glucose co-transporter-2. SGLT2 is a sodium-solute cotransport protein located in the kidney proximal tubule that reabsorbs the majority of glomerular-filtered glucose.(List *et al.*, 2009)

Dapagliflozin is SGLT2 selective and contains a C-glucoside for enhanced in vivo stability, both of which contribute to a longer half-life and consistent pharmacodynamic efficacy. In healthy volunteers and type 2 diabetic patients, dapagliflozin causes consistent rates of glucosuria, totaling to about 70 g glucose excreted from body daily. Individuals with familial renal glycosuria, which is caused by genetic mutations in the SGLT2 gene, have mostly benign phenotypes, with normal life expectancies and no long-term renal degeneration or known health consequences. (List *et al.*, 2009)

Dapagliflozin is unique in that it has an insulin-independent effect on lowering glucose reabsorption, notably by the proximal tubule of the kidney, allowing more glucose from plasma to be eliminated into urine. Dapagliflozin would improve glycemic control without the side effects of traditional antidiabetic medications on body weight, blood pressure, or lipids, according to recent research, making it advantageous to combine conventional antidiabetic drugs with dapagliflozin in the treatment of T2DM. (Sun *et al.*, 2014)

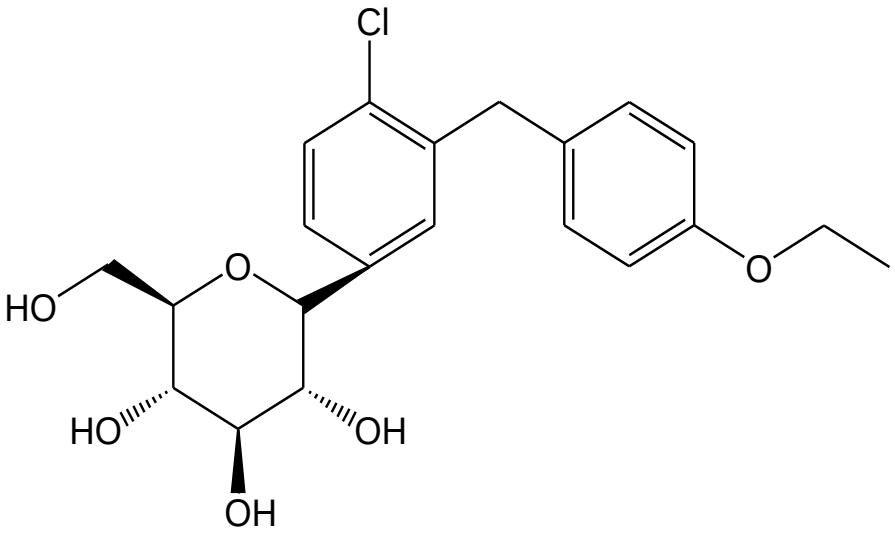
Dapagliflozin was approved in the United States on January 8, 2014, and is also available in 38 other countries, including Europe, under the brand name Forxiga (Bristol-Myers Squibb Company, Middlesex, UK) [AstraZeneca, 2012; Bristol-Myers Squibb Company, 2014]. (Anderson, 2014) dapagliflozin has additional beneficial in the weight loss, which is induced by the fluid loss in the initial stage of treatment and subsequently net calorie deficit (200–300 kcal per day). Studies on dapagliflozin have demonstrated efficacy in monotherapy as well as in combination with oral antihyperglycemic agents and insulin.

1.2. Mechanism of action of dapagliflozin



mechanism of action of dapagliflozin

1.3 Structure of Dapagliflozin



Chemical structure of dapagliflozin

Table 2: Combination of dapagliflozin with other antidiabetic drugs

Sr.	Brand Name	API(S)	Available Dosage(mg)	References
1	FORXIGA	DPG	5/10	(Ganorkar *et al.*, 2021)
2	GLEDEPA	DPG	10	(Ganorkar *et al.*, 2021)
3	OXRA	DPG	10	(Ganorkar *et al.*, 2021)
4	OXRAMET XR	DPG/MET	10/500 10/1000 5/1000	(Ganorkar *et al.*, 2021)
5	GLEDEPA MET XR	DPG/MET	10/500 10/1000	(Ganorkar *et al.*, 2021)
6	XIGUDO	DPG/MET	10/500 10/1000 5/500 5/1000	(Ganorkar *et al.*, 2021)
7	QTERN	DPG/SXG	10/5	(Ganorkar *et al.*, 2021)
8	QTERNMET XR	DPG/MET/SXG	2.5/2.5/1000 5/2.5/1000 5/5/1000 10/5/10000	(Ganorkar *et al.*, 2021)

1. Pharmaceutical Formulation of Dapagliflozin with other combinations

Combination of Dapagliflozin with other antidiabetic drugs: Compared to single drug therapy or oral monotherapy the use of combinational therapy results in more reduction of blood glucose level. In addition, increasing line of evidence suggests that patients who are not taking insulin, for those patients combination therapy involving oral anti-diabetic agents with different mechanisms of actions may be effective in controlling blood glucose levels. (Kazi *et al.*, 2021)

1.1. Coadministration of Dapagliflozin with Metformin: In terms of glycemic control, dapagliflozin and metformin have separate but complementary modes of action. The combination of dapagliflozin with metformin offers a novel treatment option for type 2 diabetes patients who are unable to achieve satisfactory glycemic control with metformin alone. (Bailey *et al.*, 2010)

Mechanism of action of Metformin: Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Combination therapy with dapagliflozin, which works through a non-insulin hypoglycemic mechanism, helps metformin work better and minimizes the risk of hypoglycemia. The PK parameters of dapagliflozin with metformin are unaffected when compared to dapagliflozin alone, such as maximum plasma concentration and area under the plasma concentration. Furthermore, dapagliflozin has no influence on the PK of medicines given together. (Tan and Hu, 2016)

Safety: The safety data from reported studies showed that coadministration of dapagliflozin and metformin did not increase safety issues compared with dapagliflozin or metformin monotherapy. Marketed Formulation available in combination of Dapagliflozin plus Metformin are Xigduo XR (dapagliflozin/metformin hydrochloride extended-release), OXRAMET XR, GLEDEPA MET XR.

1.2. Coadministration of Dapagliflozin and Saxagliptin:

DPP-4 inhibitors exert their anti-hyperglycemic action by increasing insulin levels (in a glucose-dependent manner) and decreasing glucagon concentration in the blood; sodium glucose co-transporter-2 inhibitors act by enhancing renal glucose excretion. (Garnock-Jones, 2017)

Combination of SGLT-2 inhibitors and DPP-4 inhibitors may also result in other clinically useful effects in patients with T2DM (e.g., bodyweight management). Fixed-dose combinations offer the benefits of simplifying the administration regimen, when compared with separately dispensed or single therapy of individual drugs, and may improve treatment compliance. (Garnock-Jones, 2017)

Class characteristics for DPP-4 inhibitors include being generally well tolerated, despite an increased risk of immune-mediated dermatological events and acute pancreatitis. characteristics for SGLT2 inhibitors include decreased body weight and blood pressure, although they also carry increased risks of genitourinary infections and volume depletion .(Garnock-Jones, 2017)

Saxagliptin was first introduced in the United Kingdom and the United States in 2009. Dapagliflozin was first introduced in the United Kingdom in 2012, and then in the United States in 2014. (Williams and Stephens 2015).

Mechanism of action of Saxagliptin: Saxagliptin inhibits the activity of dipeptidyl peptidase-4, DPP-4 is an enzyme that inactivates and degrades incretin hormones, cytokines and other peptides. Released in response to food, incretin hormones potentiate insulin release and decrease glucagon production, reducing serum glucose level.

The first fixed-dose combination of a DPP-4 inhibitor and an SGLT2 inhibitor to be licensed in the Europian Union to improve glycemic control in individuals with T2DM is saxagliptin plus dapagliflozin (Qtern). (Garnock-Jones, 2017)

In fasting, healthy volunteers, the geometric mean ratios of maximum plasma concentration (C_{max}), plasma AUC from time zero to the time of the last quantifiable concentration (AUCT), and plasma AUC from time zero to infinity (AUC?) were all between 0.80 and 1.25; the 90 percent CIs for the geometric mean ratios of maximum plasma concentration (C_{max}), plasma AUC from time zero to the time of the last quantifiable concentration (AUCT), and plasma AUC from time zero to Saxagliptin/dapagliflozin treatment with meals has no clinically significant influence on the pharmacokinetics of any monocomponent. There was no variation in the pharmacokinetics of saxagliptin or dapagliflozin between healthy volunteers and T2DM patients. (Garnock-Jones, 2017)

Dosage and Administration of Saxagliptin plus Dapagliflozin. In the European Union, oral saxagliptin plus dapagliflozin tablets are indicated for the improvement of glycemic control in adults with T2DM, either when metformin and/or a sulfonylurea plus a monocomponent of saxagliptin/dapagliflozin provides inadequate glycemic control, or when the patient is already receiving the free combination of saxagliptin plus dapagliflozin, A single saxagliptin/dapagliflozin 5/10 mg tablet should be taken once in a day, with or without food.

Safety: The coadministration of saxagliptin and dapagliflozin has a comparable safety profile to that observed with saxagliptin or dapagliflozin alone.(Garnock-Jones, 2017)

Marketed Formulation available in combination of Dapagliflozin plus saxagliptin is QTERN.

1.3. Coadministration of Dapagliflozin with Sitagliptin: Dapagliflozin and Sitagliptin have the potential to help people with type 2 diabetes achieve glycemic control while avoiding hypoglycemia and weight gain.

Sitagliptin is an orally active, strong dipeptidyl-peptidase inhibitor that was recently licensed for the treatment of type 2 diabetes (listed in top 20 drugs in 2017).

Mechanism of action of Sitagliptin: Like other DPP-4 inhibitors, its mechanism of action is by increasing glucagon- like peptide-1 incretin hormones and gastric inhibitory poly-peptide, it is effective in lowering HbA1c, and glucose (during fasting as well as postprandial) in monotherapy and in combination with other oral antidiabetic agents, It stimulates insulin secretion when hyperglycemia is present and inhibits glucagon secretion.

There is no commercially available combination of Dapagliflozin and Sitagliptin, but one study uses self-nanoemulsifying drug delivery systems to produce an oral combined dose form for sitagliptin and dapagliflozin (SNEDDS). The SNEDDS were created using bioactive medium-chain/long-chain triglycerides oil, mixed glycerides, and nonionic surfactants. SNEDDS including black seed oil demonstrated good self-emulsification and transparency. Using SNEDDS, a combined dose of sitagliptin and dapagliflozin could be a possible oral pharmaceutical product for improving type 2 diabetes mellitus treatment. (Kazi *et al.*, 2021)

2. CONCLUSION

Dapagliflozin may serve as a first-line option for patients who have inadequate response to metformin or whom first-line agent (e.g., metformin) is contraindicated, but has several limitations that may limit its use first line in the general T2DM patients. combination therapy using other antidiabetic drugs with complementary mechanisms of action is recommended for improving glucose control. Compared with single therapy of SGLT2, the combination therapy resulted in a greater improvement in glycemic control and body weight reduction but no difference in blood pressure.

As a combination of an SGLT-2 and a DPP-4 inhibitor has previously been shown to lead to superior improvements in glycemic control than with either agent alone. There was no difference in the safety measures between high and low dose of SGLT2 inhibitor with other antidiabetic drugs.

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