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Review Article

Detail review on pharmacokinetic parameters, efficacy and safety of Ertugliflozin

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ABSTRACT

Type 2 diabetes mellitus is a complex and chronic metabolic condition affecting 463 million people over all the word and is projected to affect 700 million by 2045. Type 2 diabetes mellitus is a prevalent, progressive disease with a need for innovative therapeutic agents to continue to advance disease management. SGLT2 inhibitors are newer, potent, anti-diabetic agents, which are inhibiting glucose reabsorption by Sodium glucose co-transporter inhibitors and increasing urinary glucose excretion from kidney. Treatment in type-2 diabetic mellitus patients with SGLT 2 inhibitors like Ertugliflozin used as a mono therapy or combination therapy with other oral anti-diabetic agents. In the summary data concerning about its chemistry, Pharmacokinetic, efficacy and safety profile of ertugliflozin as alone without addition to other oral hypoglycaemic agents of type-2 diabetes mellitus. Base on clinical trial, ertugliflozin effectively reduce glycolated haemoglobin (HbA1c), body weight and blood pressure on the type-2 diabetic patients.

INTRODUCTION

Diabetic is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys and nerves. There is a globally agreed target to halt the rise in diabetes and obesity by 2025. About 422 million people worldwide have diabetes, the majority living in low- and middle- income countries, and 1.5 million deaths are directy attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades.[1] The continued rise is largely due to an upsurge in type 2 diabetes and related risk factors, which include rising levels of obesity, unhealthy diets and widespread physical inactivity. However, levels of childhood-onset type 1 diabetes are also

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on the rise. Up to 50% of the people with Type 2 diabetes remain undiagnosed for a variable length of time and may develop complications. Therefore, most guidelines recommend screening for T2D in people above 40 to 45 years of age and/or with high risk factors such as family history of diabetes, excess weight, abdominal obesity and hypertension.[2] Approximately 4.2 million adults will die as a result of diabetes and its complications in 2019. This is equivalent to one death every eight seconds. Globally, 11.3% of deaths are due to diabetes. Almost half of these deaths are in people under 60 years of age. Half of the 463 million adults living with diabetes today are unaware that they have the condition, and are therefore at high risk of developing serious diabetes related complications. SGLT2 inhibitors are an adequate agent to add on to metformin for combination therapy.[3] The SGLT2 inhibitors are placed on a par with sulfonylurea, thiazolinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) inhibitors, and basal insulin. The ADA recommends selecting a drug class based on specific effects and patient factors. Diabetes is the leading cause of kidney disease. About 1 out of 4 adults with diabetes has kidney disease. The main job of the kidneys is to filter wastes and extra water out of your blood to make urine. Your kidneys also help control blood pressure and make hormones that your body needs to stay healthy.[4] Diabetes also may cause damage to nerves in your body. This can cause difficulty in emptying your bladder. The pressure resulting from your full bladder can back up and injure the kidneys. Also, if urine remains in your bladder for a long time, you can develop an infection from the rapid growth of bacteria in urine that has a high sugar level. About 30 percent of patients with Type 1 (juvenile onset) diabetes and 10 to 40 percent of those with Type 2 (adult onset) diabetes eventually will suffer from kidney failure.

Basic Information To Sodium Glucose Co-Transporter (SGLT):

From scientists' study in the cell lining two distinct categories of glucose transporters are present, 1) Glucose transporters (GLUTs) and 2) Sodium-glucose co transporters (SGLTs). GLUTs are passive transporters where the substrate follows its concentration gradient without the use of energy.[5] In contrast, SGLTs are secondary-active transporters that utilize the energy of one substrate going down the concentration gradient to drive the transport of the second substrate uphill, hence coupling glucose transport to the inwardly-directed sodium gradient. In humans, there are six SGLTs and 14 GLUTs in total.[6,7] Three of these glucose transporters have been found to be responsible for the reabsorption of glucose at the proximal tubule: SGLT1, SGLT2 and GLUT2.[8] SGLT1 is found mostly in the small intestine and kidney while SGLT2 is found almost exclusively in the kidney.[9] SGLT2 is a low-capacity, high-affinity glucose transporter while SGLT1 is high-capacity, low-affinity.[10] SGLT2 is (gliflozins) also seem to provide important cardioprotective benefits, although the mechanism is still unknown.[11] Treatment with gliflozins induces a switch in energy source from glucose to fat, leading to two main metabolic consequences; a reduction in glucose oxidation and an increase in free fatty acid oxidation with the stimulation of ketogenesis.[12] The selection of b-hydroxybutyrate instead of fatty acids by the heart may enhance the efficiency at the mitochondrial level and may be responsible for the improved myocardial performance.[13] Gliflozins may inhibit myocardial ketone oxidation with a consequent reduction in Acetyl-CoA. This leads to a reduction of detrimental hyper- acetylation of mitochondrial enzymes and to increased pyruvate oxidation derived from glucose. These two actions might be responsible for an improvement in mitochondrial energy production and myocardial

metabolism.SGLT2is are also known to induce short- and long-term reduction in BP.[14] As expected, considering their mechanism of action, SGLT2is are effective in reducing both systolic (SBP) and diastolic blood pressure (DBP), likely due to glucose-driven osmotic diuresis, as shown by increases in haematocrit and decreases in body weight. Osmotic diuresis leads to the excretion of glucose and water, resulting in increased urinary output ranging from ~110 to 470 mL/day.[15]

♦ Mechanism of Action of SGLT Inhibitors

Glucose is freely filtered by the glomeruli in kidneys but maximum amount of glucose reabsorption occurs in proximal tubules in kidneys. There is an active transport mechanism whereby glucose is reabsorbed with sodium via sodium dependent glucose co transporter protein 1 & 2 that called SGLT1 and SGLT2. Na^+ / K^+ ATP pumps on the basolateral membrane of tubular cells provided the energy for this process. Sodium and glucose transfer into tubular cell and glucose subsequently returned into blood via GLUT transport. Normally healthy person reabsorb glucose about 375 mg/min by this way and excess glucose is excreted in urine.[16]

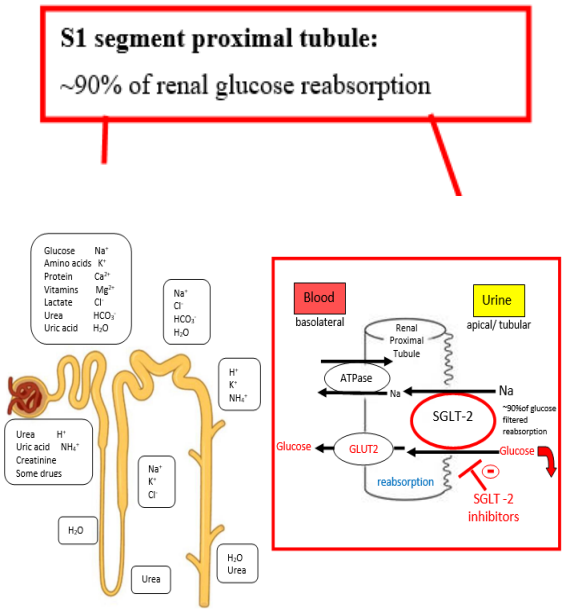

Figure 1: Mechanism of action of SGLT 2 Inhibitors.

SGLT inhibitors suppress that mechanism leading to reduce reabsorption of glucose into blood stream and maximum loss of glucose if occur in urine. These inhibitors also affect the level of sodium reabsorb only 10% glucose in kidneys while 90% glucose reabsorb by SGLT2 so inhibit SGLT2 maximum in kidneys only [Fig. 1]. SGLT2 inhibitors differ from other oral anti hyperglycaemic agents by offering an insulin-independent mechanism of action. They reduce blood glucose though glycosuria and natriuresis initiated by the inhibition of glucose reabsorption at the proximal tubule of the kidney.[17] SGLT-2 inhibitors have been shown to be effective at lowering haemoglobin A1c levels, improving weight loss and lowering blood pressure. They carry a low risk of hypoglycaemia.[18]

♦ Drug used in SGLT inhibitors

Medicines in the SGLT2 inhibitor class include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. In addition, empagliflozin is approved to lower the risk of death from heart attack and stroke in adults with type 2 diabetes and heart disease. Untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease.

There are also combination drugs available for patients with type 2 diabetes. They include either metformin or a dipeptidyl peptidase-4 (DPP-4) inhibitor as the second active drug. The SGLT2 inhibitors differ mostly in their binding, affinity and selectivity for SGLT transporters.[19]

Several SGLT inhibitors have currently been approved in Europe, USA, Japan and India. They are summarized in Table 1.

Sr. No.	Name of drug	Approval of drug
1	Canagliflozin	FDA in March-2013
2	Dapagliflozin	FDA in January 2014
3	Empagliflozin	FDA in August 2014
4	Ertugliflozin	FDA in December 2017
5	Ipragliflozin	Japan in January 2014
6	Luseogliflozin	Japan in March 2014
7	Remogliflozin etabonate	India in 2019
8	Tofogliflozin	Japan in March 2014

Ertugliflozin:

Ertugliflozin is a potent antidiabetic drug belongs to selective inhibitors of sodium-dependent glucose co- transporters (SGLT) and more specifically the type 2 diabetics which is responsible for about 90% of the glucose reabsorption from glomerulus.[20] It was FDA approved as monotherapy and in combination with sitagliptin or metformin hydrochloride on 22 December 2017 [Fig. 2].

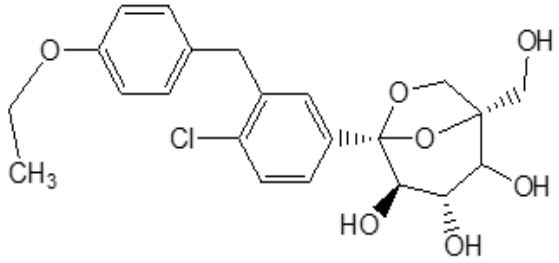

Figure 2: Structure Of Ertugliflozin

Chemistry

Molecular weight is 436.89g/mol and chemical formula is $C_{22}H_{25}ClO_7$. Chemically ertugliflozin is (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[21] in which 6,8-dioxabicyclo [3.2.1] octane- 2, 3, 4- triol is called as a 1, 6 anhydro- D- galactose. This 1, 6 anhydro- D- galactose is a carbohydrate formed by alkaline hydrolysis of phenyl- β- galactosides. At 6 and 8 position of bicycle [3.2.1] octane add oxygen in place of carbon and form 6, 8- dioxabicyclo [3.2.1] octane. Addition of hydroxyl group at 2, 3, 4 position of 6, 8- dioxabicyclo [3.2.1] in ertugliflozin which is responsible for the metabolism.

♦ Pharmacology

Absorption-

From clinical data, ertugliflozin is well absorbed in orally and its oral bioavailability is 70-90%. Peak plasma concentration of ertugliflozin occur within 0.5- 1.5 hrs after administration. 15 mg oral dose given in healthy volunteers and reported the value of Cmax and AUC of 268ng/ml and 1193ng/ml respectively.[20]

Steady state volume of distribution after IV administration of ertugliflozin is 85.53L. Plasma protein binding of ertugliflozin is 93.6% and it is independent to plasma concentration. The blood-plasma concentration of ertugliflozin is 0.66.

Metabolism-

Ertugliflozin is metabolised in liver by monohydroxylation, O- demethylation and glucuronidation reaction. In vitro studies shows that this metabolism has formed 8 different

metabolites which is found in plasma, Urine and faeces. Ertugliflozin is metabolised by hydroxylation reaction and it formed M1b ertugliflozin, M1a ertugliflozin and M3 ertugliflozin. M1a ertugliflozin and M1b ertugliflozin both are isomer while in M3 ertugliflozin hydroxyl group attach at 3 positions on 4-ethoxy phenyl ring of ertugliflozin. In Demethylation reaction of ertugliflozin was formed M2 ertugliflozin. Ethoxy group ertugliflozin are convert to hydroxyl group by demethylation reaction and further M2 ertugliflozin goes to 3-O and 4- O glucuronidation reaction. Glucuronidation reaction occurs in presence of UDP-glucuronosyltransferase 1A9 and UDP-glucuronosyltransferase 2B7 enzyme. They formed M5a ertugliflozin and M5b ertugliflozin respectively.

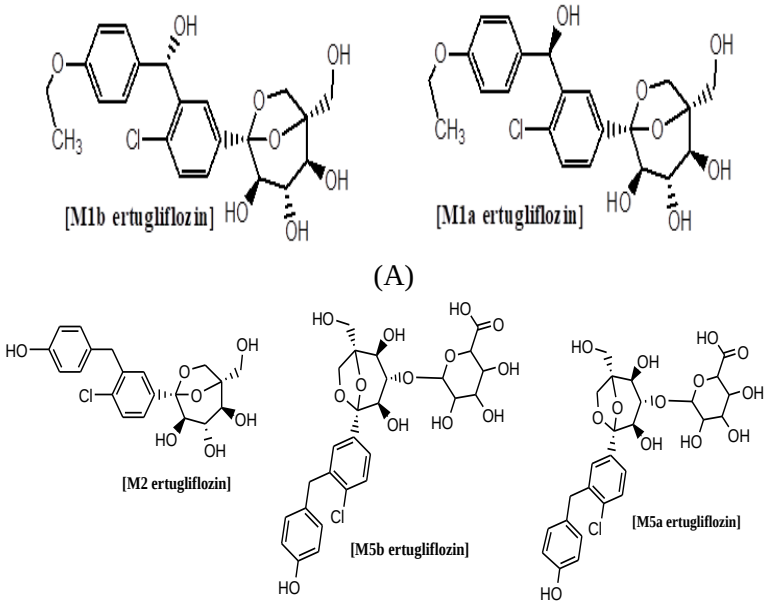

Figure 3: Metabolism of ertugliflozin: A) Hydroxylation Reaction B) Demethylation Reaction.

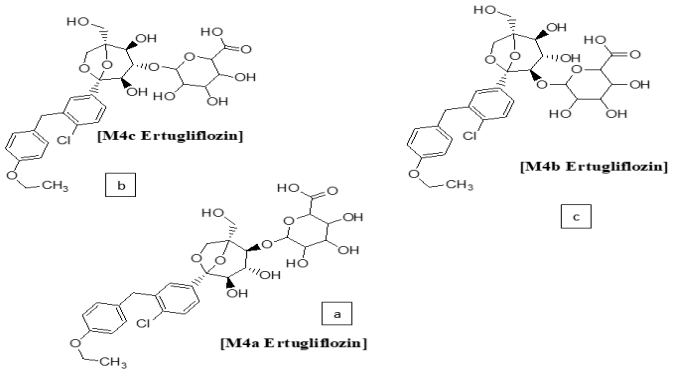

Figure 4: Hepatic Metabolism of ertugliflozin: (a) Ertugliflozin- 4- β- O- glucuronide (M4a) (b) Ertugliflozin- 3- β- O- glucuronide (M4c) (c) Ertugliflozin- 2- β- O- glucuronide (M4b)

Excretion-

The mean plasma concentration of intravenous route of administration having 100 ug doses was 11.2 L/hr. Oral administration in healthy subjects, 40.9% and 50.2% of the metabolite was eliminated in faeces and urine respectively. The eliminated dose in urine was composed of seven different major metabolites of ertugliflozin and the

unchanged ertugliflozin as a minor metabolite. The elimination rate in faeces was depending on the bowel movements of each patient but 98.5% of the eliminated dose in faeces was obtained after 168 hours of initial dosage. This eliminated dose was formed mainly by unchanged ertugliflozin and three other minor metabolites. The mean plasma elimination half-life is long about 11-17hrs.[23]

Efficacy Of Ertugliflozin:

♦ Blood Glucose level

Ertugliflozin treatment was reported as placebo-adjusted least-squares (LS) mean change from baseline average HbA_{1C} reduction after week 26. Ertugliflozin dosage daily 5 mg and 15 mg reduced the HbA_{1C} significantly compare with placebo -0.8% and -0.9% respectively. ($P< 0.001$ for both comparisons). The percentage of patient population receive ertugliflozin had an HbA1c less than 7 % at 26 weeks compare with placebo. A total of 15.3 %, 32.2% and 38.7 % of participants achieved an HbA1c of less than7 % in the placebo [Fig. 5A], ertugliflozin 5mg and ertugliflozin 15 mg groups respectively.[23-25]

♦ Body Weight

reatment with 5 mg and 15 mg dose of ertugliflozin resulted in a greater reduction in body weight from baseline place than placebo in 26 weeks clinical studies. The least square mean change of body weight from baseline was -1.4 kg for placebo, -3.2kg for 5 mg dose of ertugliflozin and -3.2 kg for 15mg dose of ertugliflozin [Fig. 5B]. From clinical data, almost 1/3 of patients who received dose of ertugliflozin reduced body weight greater or equal to 5% from baseline at 26 weeks compare with placebo.[23,26]

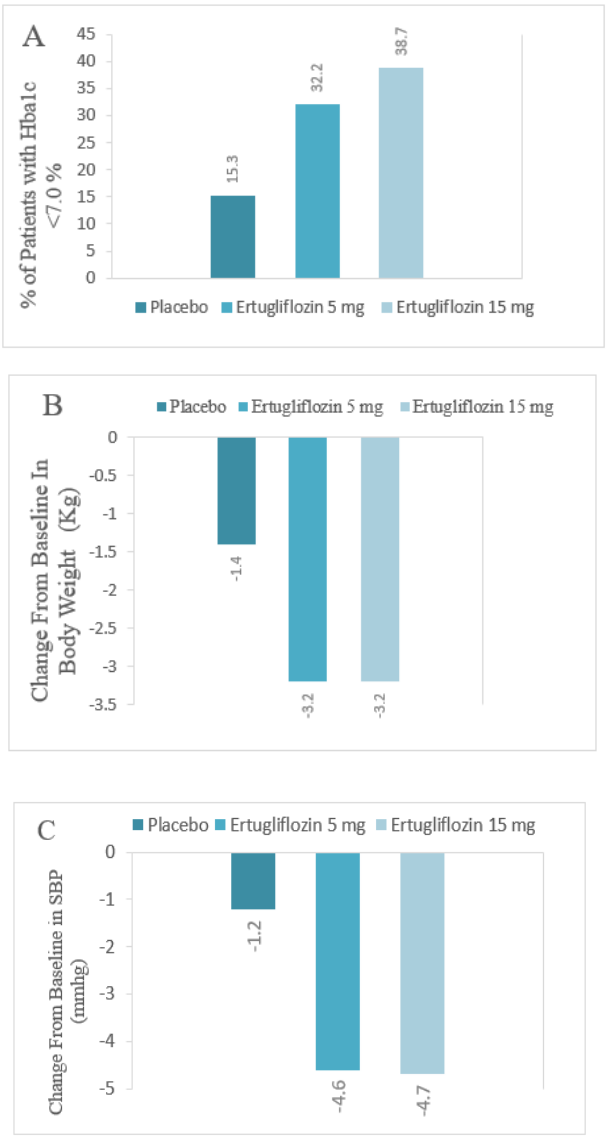

Figure 5: (A) Percentage of patients with HbA1c <7.0% at Week 26 in the pooled population. (B) Change from baseline in body weight at Week 26 in the pooled population. (C) Change from baseline in sitting systolic blood pressure (SBP) at Week 26 in the pooled population.

Blood Pressure

After 26 weeks, treatment of ertugliflozin 5 mg and 15 mg resulted a greater reduction from baseline in systolic blood pressure compare with placebo. The least square mean change of blood pressure from baseline was-1.2 mmHg for placebo, -4.6 mmHg for ertugliflozin 5 mg and -4.7mmHg for 15 mg ertugliflozin [Fig. 5C]. The percentage of treated patients with systolic blood

pressure greater or equal to 130mmHg at base line who achieved Systolic blood pressure less then 130mmHg after 26 weeks.[23-26]

Safety Information:

♦ Genital mycotic infections

Ertugliflozin has repeatedly to increases the risk of genital mycotic infections. Genital mycotic infections in Women (genital candidiasis, vaginal infection, vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis, etc.) occurred in 4.4%, 13.6%, and 14.3% of female participants in the placebo, ertugliflozin 5-mg, and ertugliflozin 15-mg groups. While Genital mycotic infections in men (balanitis candida, balanoposthitis, genital infection, etc.) occurred in 0.6%, 3.2%, and 5.5% of male participants, respectively in trials with SGLT2 inhibitors. If the Patients are taking ertugliflozin who have a history of genital mycotic infections so monitored and treated appropriately.[23,27]

♦ Urinary tract infections

Excretion of Urinary glucose may be associated with an increased risk of urinary tract infections. The incidence of urinary tract infections was not identical different in the ertugliflozin 5 mg and 15 mg groups (4.0% and 4.1%) and the placebo group (3.9%). Diabetes patients have significantly greater Urinary tract infections compared to non-diabetic patients.[28] Diabetic patients at high risk for Urinary tract infections contraction include those with poor glycemic control (e.g., A_{1C}> 8.5%), those of advanced age, those who are female, and those with a history of UTI within the previous two years.[29] While only minor cases have been reported in ertugliflozin, Urinary tract infections should be monitored carefully and treated promptly. Temporary interruption of ertugliflozin should be considered when treating pyelonephritis or urosepsis.

♦ Ketoacidosis

In clinical trial of ertugliflozin rare cases of Diabetic Ketoacidosis, including life-threatening and fatal cases, have been reported. Diabetic Ketoacidosis is not more likely to occur with higher doses of ertugliflozin. Ketoacidosis has occurred in patients treated with SGLT2 inhibitors without the presence of profound hyperglycemias.[30] The risk of diabetic ketoacidosis must be considered a non-specific symptom such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. If patients have suspected or diagnosed the diabetic ketoacidosis then treatment with ertugliflozin should be discontinued immediately. Measure the level of blood ketone form urine. Treatment with ertugliflozin may be restarted when the ketone value is normal and patient's condition has stabilised. Patents have type-1 diabetes and they are treated with SGLT-2 inhibitors so most of patients occur Ketoacidosis. Ertugliflozin should not be used for treatment of type-1 diabetics.

♦ Hypotension/ Volume depletion

Ertugliflozin causes an osmotic diuresis which may lead to contract intravascular volume. Hence, symptomatic hypotension may occur after ertugliflozin treatment that is particularly occur in patients with impaired renal function, older patients (≥ 65 years), patients take diuretics treatment or patients on anti-hypertensive therapy with a history of hypotension. Ertugliflozin induces an osmotic diuresis and increases serum creatinine and decreases eGFR which may lead to fluid loss. At that condition, carefully monitor volume status (e.g., physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving ertugliflozin.[23]

♦ Impairment in renal function

Form studies, ertugliflozin's safety and efficacy are dependent on renal function and efficacy is reduced in patients who have moderate renal impairment and absent in patients with severe

renal impairment. Hence, clinical decisions should be based on eGFR rather than on estimated creatinine clearance (CrCl). Initially, Ertugliflozin should not be started in patients with an eGFR below 60 ml/min/1.73 m2 or CrCl below 60 ml/min. Ertugliflozin should be discontinued when eGFR is value below 45 ml/ min/ 1.73 m2 or CrCl is level below 45 ml/min due to a reduction of efficacy. , the antihyperglycemic effects of ertugliflozin are compromised in patients with moderate to severe kidney impairment. Monitoring of renal function is recommended,[31] It is prior to ertugliflozin initiation and periodically during treatment. More frequently in patients with an eGFR below 60 ml/ min/ 1.73 m2 or a CrCl below 60 ml/ min.

♦ Hypoglycaemia

There was no significant difference in the incidence of symptomatic hypoglycaemia between the treatment and control groups in the clinical trials of ertugliflozin. Ertugliflozin alone is not increase the risk for symptomatic hypoglycaemia, but ertugliflozin have risk incidence has been reported when it is taken in combination with insulin or insulin secretagogues.[22] Patient counselling should be considered when combining ertugliflozin with these medications.

♦ Urosepsis and Pyelonephritis

Post marketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving SGLT2 inhibitors. In clinical trial, ertugliflozin treated the pyelonephritis. SGLT2 inhibitors are increases the risk for urinary tract infections after treatment of ertugliflozin evaluate patients for signs and symptoms of urinary tract infections and treat promptly.[23,32]

♦ Lactose

Ertugliflozin tablets contain lactose monohydrate. If patients have rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose mal absorption than they should not take ertugliflozin.[33]

♦ Pregnancy

Data of clinical trial have been extrapolated from animal studies with rat while ertugliflozin has not studied in human pregnancy. Renal tubule dilatation, malformation, and mineralization occurred when ertugliflozin was administered in gestational periods that correspond to the late second and third trimesters of human pregnancy. However, package labelling indicates that ertugliflozin is not recommended in the second and third trimesters of pregnancy. From the data, it should be noted that uncontrolled diabetes is a significant cause of neonatal abnormalities and miscarriages.[23]

♦ Lactation

Ertugliflozin is present in human breast milk because the drug is found in the breast milk of nursing rats in clinical trial. Human renal development continues from the latter stages of neonatal development and through the first two years of life. Renal abnormalities have been found in gestational animal studies; it is not unreasonable to assume that exposing human infants to ertugliflozin may pose a threat to normal renal development. It is not advisable to administer ertugliflozin to nursing mothers.[23]

♦ Lower limb amputations

Form clinical studies, ertugliflozin therapy in type 2 diabetes patients with an approximately 1.2-1.6-fold increase in cases of lower limb amputation has been observed in patients treated with ertugliflozin. Lower limb amputation (primarily of the toe) has also been observed in long-term clinical studies with another SGLT2 inhibitor. Before initiating ertugliflozin, consider factors in the patient history that may increase the risk for amputation.[23,31]

CONCLUSION:

Diabetes mellitus is associated with cardiovascular risk but newer anti-diabetic class SGLT inhibitors

were improved cardiovascular profile in type 2 diabetic patients. Ertugliflozin have 70- 90 % bioavailability and d93.6 % Plasma Protein binding. It reduces HbA1c 0.8 % by inhibiting the absorption of glucose from proximal tubule of the kidney. Ertugliflozin have also favourable effects on body weight and blood pressure, both are reduced 3.2 kg and 4.6mmHg respectively. All data are having ertugliflozin 5 mg and 15 mg over 26 weeks across placebo-controlled trials in different therapies. Urinary track and genital infection as well as Diabetic Ketoacidosis and Lowe limb amputation are most common adverse effect.

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