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New Drug Update

Ertugliflozin: a novel anti-diabetic drug

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ABSTRACT

Diabetes Mellitus is a disorder of global proportion. Despite various treatment modalities presently being available, yet the desired glycaemic control and patient outcomes have not been achieved completely. Sodium glucose co-transporter type 2 inhibitors (SGLT2 inhibitors) are one such promising group of emerging drugs in diabetes treatment. Ertugliflozin prevents the reabsorption of glucose by inhibiting sodium-glucose cotransporter-2 (SGLT2) at proximal convoluted tubules. Ertugliflozin is available as 5mg and 15mg tablets. Ertugliflozin has been related to genital mycotic infections and urinary tract infections. Benefits of Ertugliflozin include better control on blood glucose, body weight and blood pressure.

Keywords: Diabetes mellitus, Ertugliflozin, SGLT2 inhibitor

INTRODUCTION

Diabetes mellitus is a disorder of global proportion. Despite various treatment modalities presently being available, yet the desired glycaemic control and patient outcomes have not been achieved completely. Hence, there is an unmet need to develop new drugs which would benefit most patients.

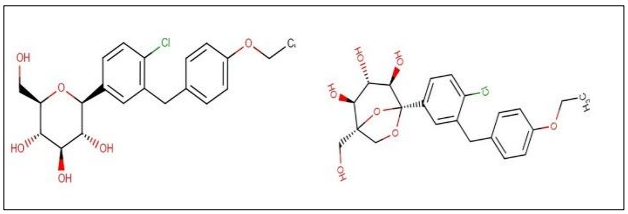
Sodium glucose co-transporter type 2 inhibitors (SGLT2 inhibitors) are one such promising group of emerging drugs in diabetes treatment. Manufacturing and processing of SGLT2 inhibitor drugs have been a challenge for the pharmaceutical industry. Ertugliflozin is the latest in the series to be approved by the US Food and Drug Administration for type 2 diabetes in December 2017.

In addition to euglycaemia, the drug benefits patients in control of systolic blood pressure and body weight, which is of paramount importance.

The European Medicines Agency has also opined that benefits outweigh the risks when Ertugliflozin is prescribed to T2DM patients.[1]

CHEMICAL STRUCTURE OF ERTUGLIFLOZIN

Ertugliflozin is chemically ($C_{22}H_{25}ClO_7$): (1S,2S,3S,4R,5S)-5-[4-Chloro-3-(4-ethoxybenzyl) phenyl]-1-hydroxymethyl6,8-dioxabicyclo[3.2.1] octane-2,3,4-triol.[2] The molecular structure of Ertugliflozin is depicted in Figure 1.[2]



Dapagliflozin- a representative SGLT2 inhibitor

Ertugliflozin

Figure 1: Molecular structure.

MECHANISM OF ACTION

Ertugliflozin prevents the reabsorption of glucose by inhibiting sodium-glucose cotransporter-2 (SGLT2) at proximal convoluted tubules (Figure 2). This leads to excessive excretion of glucose in urine, leading to a fall in blood glucose levels. It thereby, reduces glucose toxicity, improves insulin sensitivity and β-cell function.

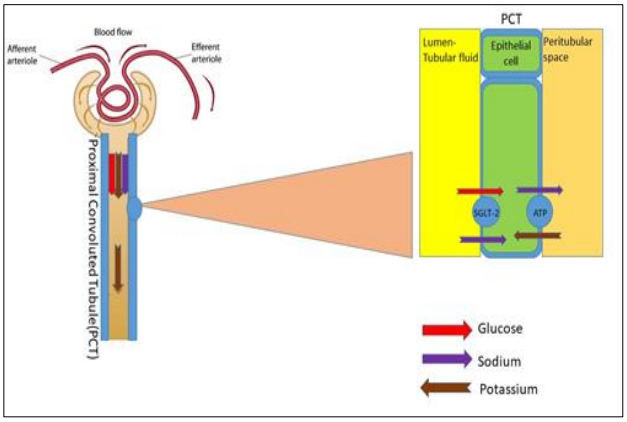


Figure 2: Site of action of Ertugliflozin.

PHARMACOKINETICS

Sodium-glucose cotransporter-2 (SGLT2) inhibitor, Ertugliflozin is given orally. It is well absorbed and has an oral bioavailability of 70-90%. Tmax (median) is 1 hour (fasting state) and 2 hours (after high-fat meal). It is metabolised primarily by UGT1A9- and UGT2B7-mediated O-glucuronidation to inactive metabolites. Elimination is through urine (50%) and faeces (41%). Half-life is greater than16 hours.

CLINICAL EFFICACY

Summarised efficacy of Ertugliflozin as per clinical trials is depicted in Table 1.

VERTIS program

Ertugliflozin is being evaluated in many international multicentre clinical trials, belonging to the VERTIS program studies (eValuation of Ertugliflozin efficacy and safety). In these studies, Ertugliflozin has been evaluated as monotherapy and as add-on/combination therapy with other anti-diabetic drugs.[3]

The VERTIS MONO study is a multicentre, randomized, parallel-group phase III clinical trial of 52-weeks.[4] It was conducted in two periods of 26-weeks each, first being double-blind, placebo-controlled followed by an active-controlled treatment period. A total of 461 participants were randomized and received a minimum of one dose of study medication, Ertugliflozin 5 or 15mg, or placebo. The mean age of the study participants was 56.4years. Mean baseline HbA1c was 8.21% and the mean period of T2DM was ~5years. At screening, ~52% of the randomized population were receiving treatment with one anti-diabetic agent, which was discontinued at week 26, the placebo-adjusted least squares (LS) mean HbA1c changes from baseline were -0.99% and -1.16% for the Ertugliflozin 5 and 15mg doses respectively ($p = 0.001$ for both doses). Ertugliflozin 5 and 15mg were able to achieve target levels of 7.0% HbA1c in higher number of patients, compared with the placebo group. Both doses of Ertugliflozin significantly lowered fasting and postprandial plasma glucose levels. The placebo adjusted LS mean body weight changes from baseline were -1.76, and -2.16kg for Ertugliflozin 5 and 15mg, respectively. No statistically significant reduction in systolic blood pressure (SBP) was observed for the Ertugliflozin 15mg group vs placebo. Ertugliflozin tolerability was good throughout the 26-week period of phase A, though genital infections were more. The proportions of participants discontinuing study medication in phase A were 22.2%, 14.1%, and 13.8% for placebo, Ertugliflozin 5mg, and Ertugliflozin 15mg respectively.

In the VERTIS MET trial, Ertugliflozin was studied additionally to metformin monotherapy (1,500mg/d for 8 weeks) in poorly controlled T2DM patients (HbA1c, 7.0%-10.5%).[5] A total of 621 participants were randomized 1:1 to placebo or Ertugliflozin 5 or 15mg/d. The change of HbA1c from baseline to the end of the study (at week 26) was evaluated. Variations from baseline in FPG (fasting plasma glucose), BW (body weight), SBP/ diastolic blood pressure (DBP) and the percentage of patients reaching 7.0% HbA1c were evaluated. Change in bone mineral density (BMD) was the adverse event evaluated.

Further, the incidence of urinary tract infections and symptomatic hypoglycemia was higher with Ertugliflozin. The incidence of hypovolaemia AEs was similar across groups. Ertugliflozin had no adverse impact on BMD at week 26.

In the VERTIS Sita 2 trial, the authors enrolled patients with HbA1c between 7.0% and 10.5%, along with metformin 1,500mg/day and sitagliptin 100mg/day.[6] Total 464 randomized patients were administered once daily dose of Ertugliflozin 5mg, 15mg or placebo. HbA1c at baseline and after 26 weeks were evaluated, treatment was

continued till week 52. After 26 weeks, HbA1c was reduced by -0.7%, and -0.8% with Ertugliflozin 5 and 15 mg respectively (both p = 0.001) compared with placebo. Moreover, 17.0% of patients receiving placebo, 32.1% receiving Ertugliflozin 5mg, and 39.9% receiving Ertugliflozin 15mg reached target of 7.0% HbA1c. The positive effects of Ertugliflozin on glycaemic management, BW, and SBP were observed through week 52. UTI, symptomatic hypoglycemia, and hypovolaemia incidence were similar among groups.

Table 1: Clinical trials on Ertugliflozin.

Trial name	Patients number	Time in weeks	Treatments	Summary
VERTIS MONO[4]	461	26+26	Ertugliflozin 5mg Ertugliflozin 15mg Placebo phaseA Metformin phaseB	Multicentric RCT with placebo and active comparator. Results showed decrease in blood glucose, body weight and SBP
VERTIS MET[5]	621	26+26	Ertugliflozin 5mg Ertugliflozin 15mg Placebo	Multicentric RCT with placebo. Results consistent with other Vertis studies
VERTIS FACTORIAL[7]	1233	26+26	Ertugliflozin 5mg Ertugliflozin 15mg Sitagliptin 100mg (Ertugliflozin 5mg + Sitagliptin 100mg) (Ertugliflozin 15mg+Sitagliptin 100m)	Multicentric RCT with an active comparator. Results consistent with other Vertis studies
VERTIS SITA[8]	291	26	(Ertugliflozin 5mg+ Sitagliptin 100mg) (Ertugliflozin 15mg+ Sitagliptin 100m) Placebo	Multicentric RCT with placebo and an active comparator. Results consistent with other Vertis studies
VERTIS SITA 2[6]	464	26+26	Ertugliflozin 5mg Ertugliflozin 15mg Placebo	Multicentric RCT with placebo. Results consistent with other Vertis studies
VERTIS SU[9]	1,326	52	Ertugliflozin 5mg Ertugliflozin 15mg Titrated Glimepiride	Multicentric RCT with an active comparator. Results consistent with other Vertis studies
VERTIS CV study ongoing	8000	316	Ertugliflozin 5mg Ertugliflozin 15mg Placebo	Multicentric RCT with placebo. Ongoing study.

The VERTIS FACTORIAL trial confirmed that the incidence of AEs was identical across groups, except that incidence of genital mycotic infections was higher in groups treated with Ertugliflozin.[7] In the trial, the incidence of UTI was not significantly different in groups treated with Sitagliptin or a combination of Sitagliptin and Ertugliflozin. Symptomatic hypoglycemia was 2.4% with Ertugliflozin 5mg and 4.9% with a combination of Ertugliflozin 15mg and Sitagliptin. Hypovolaemia AE rates were 1.6% and 0.8% in Ertugliflozin 5 and 15mg groups respectively, and 0.33% in all other groups.

Other studies are still ongoing especially the VERTIS CV trial (cardiovascular outcomes following Ertugliflozin treatment in T2DM participants). The trial will judge the cardiovascular outcomes following treatment with Ertugliflozin in participants with T2DM and established vascular disease. Other attention-grabbing results will be obtained from the MK-8835-001 trial, "A Study of the efficacy and safety of Ertugliflozin in participants with type 2 DM with stage three chronic kidney diseases who have inadequate glycaemic control on antihyperglycemic therapy". Here, the primary aim will be to gauge the HbA1c-lowering efficacy of Ertugliflozin compared to placebo as an add-on antidiabetic agent.

ADVERSE EFFECTS

Ertugliflozin has been related to genital mycotic infections and urinary tract infections. Hypoglycemia seldom happens with an SGLT2 inhibitor alone or together with a DPP-4 inhibitor, unless the patient is on an additional

antihyperglycemic drug. Due to loss of sodium, it may cause hypovolemia, dehydration and acute kidney injury. It can conjointly cause ketoacidosis, primarily in patients with type 1 diabetes. Use of Ertugliflozin in clinical trials was related to lower-limb amputations in 0.2% of patients taking the 5mg dose and in 0.5% of those taking the 15mg dose.[10]

INDICATION

Ertugliflozin is an oral sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to enhance glycaemic management in adults with T2DM.[11]

APPROVED PREPARATIONS

The US Food and Drug Administration approved Ertugliflozin as a standalone drug and in combination with Sitagliptin or Metformin to treat T2DM.

WARNINGS AND PRECAUTIONS

Genital infections increased low-density lipoprotein-cholesterol (LDL - C), hypotension, ketoacidosis, acute kidney injury/ impairment, urinary tract infections, hypoglycemia with concomitant use of insulin and insulin secretagogues are issues of concern with the use of Ertugliflozin.[2]

DOSAGE AND ADMINISTRATION

Ertugliflozin is available as 5mg and 15mg tablets. The recommended beginning dose is 5mg once daily, taken in the morning, with or without food. In patients tolerating Ertugliflozin 5mg once daily, the dose could also be increased to 15mg once daily. No dose adjustment is required in patients with mild renal impairment.[12]

CONCLUSION

Ertugliflozin offers a unique therapeutic approach to T2DM. Benefits of Ertugliflozin include better control on blood glucose, body weight and blood pressure. Adverse effects seen are genital fungal infections and occasional hypoglycaemia. Initial studies do not show an increased risk of cardiovascular disease. However, longer period clinical studies are still essential.

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Ethical approval: Not required

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