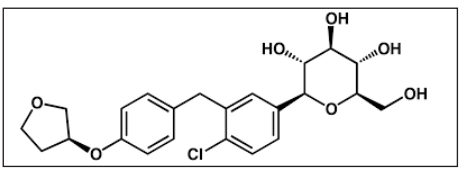
Voreta/Voreta plus Tablets*

وورِیٹا/وورِیٹا پلس ٹیبلٹس

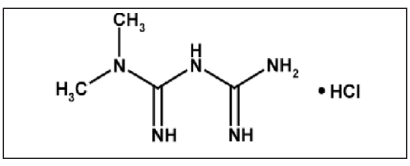
WARNING
Cases of Metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and Metformin plasma levels generally >5 mcg/mL.
Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment.
If lactic acidosis is suspected, discontinue drug and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

COMPOSITION:
Each VORETA tablet contains: Empagliflozin .....10mg & 25mg
Each VORETA PLUS contains: Empagliflozin / Metformin HCl.....5/500 , 5/1000, 12.5/500 & 12.5/1000mg

DESCRIPTION
Empagliflozin
Empagliflozin is an orally-active inhibitor of the sodium-glucose co-transporter 2 (SGLT2). The chemical name of Empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3- furanyl]oxy]phenyl]methyl]phenyl]-, (1S). Its molecular formula is C23H27ClO7 and the molecular weight is 450.91. The structural formula is:



Metformin hydrochloride
Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of C4H11N5HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of Metformin is 12.4. The pH of a 1% aqueous solution of Metformin hydrochloride is 6.68. The structural formula is:



CLINICAL PHARMACOLOGY
Mechanism of Action: VORETA PLUS combines 2 antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: Empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and Metformin, a member of the biguanide class.
***VORETA* (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.
VORETA PLUS (Metformin hydrochloride) 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.
Pharmacodynamics:
Empagliflozin
Urinary Glucose Excretion
In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of Empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg Empagliflozin and 78 grams per day with 25 mg Empagliflozin once daily.
Cardiac Electrophysiology
No increase in QTc is observed with Empagliflozin.
Pharmacokinetics
Administration of Empagliflozin Metformin under fed conditions resulted in a 9% decrease in AUC and a 28% decrease in Cmax for Empagliflozin, when compared to fasted conditions. For Metformin, AUC decreased by 12% and Cmax decreased by 26% compared to fasting conditions. The observed effect of food on Empagliflozin and Metformin is not considered to be clinically relevant.

The pharmacokinetic properties of the components of VORETA and VORETA PLUS are provided in Table 1.
Table 1 Pharmacokinetic Properties of the Components of VORETA and VORETA PLUS

Empagliflozin	**Metformin HCl**
Absorption	
After oral administration, peak plasma concentrations of Empagliflozin are reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. Systemic exposure of Empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of Empagliflozin are similar, suggesting linear pharmacokinetics with respect to time.	Single oral doses of Metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of Metformin.
Distribution	
The apparent steady-state volume of distribution is estimated to be 73.8 L based on a population pharmacokinetic analysis.	Metformin is negligibly bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound.
Metabolism	
No major metabolites of Empagliflozin are detected in human plasma and the most abundant metabolites are three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide).	Intravenous single-dose studies in normal subjects demonstrate that Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary
Elimination	
The apparent terminal elimination half-life of Empagliflozin is estimated to be 12.4 h and apparent oral clearance is 10.6 L/h based on the population pharmacokinetic analysis.	Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of Metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

THERAPEUTIC INDICATIONS
VORETA and VORETA PLUS are indicated for the treatment of adults with insufficiently controlled Type 2 Diabetes Mellitus as an adjunct to diet and exercise
- In addition to other medicinal products for the treatment of diabetes

VORETA PLUS is a combination of Empagliflozin and Metformin HCl indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing Empagliflozin or Metformin, or in patients already being treated with both Empagliflozin and Metformin.
Limitation of Use
VORETA and VORETA PLUS are not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
CONTRAINDICATIONS
VORETA and VORETA PLUS are contraindicated in patients with:
- Moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m2), end stage renal disease, or dialysis.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of serious hypersensitivity reaction to Empagliflozin or Metformin.

ADVERSE REACTIONS
Most common adverse reactions associated with Empagliflozin (5% or greater incidence) are 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.
DRUG INTERACTIONS
Drug Interactions with Empagliflozin:
Diuretics
Coadministration of Empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Insulin or Insulin Secretagogues
Coadministration of Empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia.
Positive Urine Glucose Test
Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay
Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing.
Drug Interactions with Metformin Hydrochloride
Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of Metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to Metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with VORETA PLUS may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients

Drugs Affecting Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving VORETA PLUS , the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving VORETA PLUS , the patient should be observed closely for hypoglycemia.

Alcohol

Alcohol is known to potentiate the effect of Metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving VORETA PLUS .

USE IN SPECIFIC POPULATION

Pregnancy:

VORETA and VORETA PLUS are not recommended during the second and third trimesters of pregnancy.

Lactation:

There is no information regarding the presence of VORETA and VORETA PLUS or Empagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Potential for serious adverse reactions in a breastfed infant, advise women that use of VORETA and VORETA PLUS are not recommended while breastfeeding.

Females and Males of Reproductive Potential:

Unintended pregnancy with premenopausal women as therapy with Metformin may result in ovulation in some anovulatory women.

Pediatric Use:

Safety and effectiveness of VORETA and VORETA PLUS in pediatric patients under 18 years of age have not been established.

Geriatric Use:

Because renal function abnormalities can occur after initiating Empagliflozin, Metformin is substantially excreted by the kidney, and aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients.

Renal Impairment:

VORETA and VORETA PLUS are contraindicated in patients with moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m^2).

Hepatic Impairment:

VORETA and VORETA PLUS should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Empagliflozin may be used in patients with hepatic impairment. Use of Metformin hydrochloride in patients with hepatic impairment has been associated with some cases of lactic acidosis. VORETA and VORETA PLUS are not recommended in patients with hepatic impairment.

WARNINGS AND PRECAUTIONS

Lactic Acidosis

There have been postmarketing cases of Metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension, and resistant bradyarrhythmias have occurred with severe acidosis.

Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate:pyruvate ratio; Metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If Metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of VORETA and VORETA PLUS . In VORETA and VORETA PLUS -treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated Metformin (Metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions).

Hemodialysis has often resulted in reversal of symptoms and recovery.

Hypotension

Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating Empagliflozin particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating VORETA and VORETA PLUS , assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected.

Ketoacidosis

ketoacidosis, a serious life-threatening condition require urgent hospitalization in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including Empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking Empagliflozin. VORETA and VORETA PLUS are not indicated for the treatment of patients with type 1 diabetes mellitus.

Acute Kidney Injury and Impairment in Renal Function

Empagliflozin causes intravascular volume contraction and can cause renal impairment.

Urosepsis and Pyelonephritis

There are reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including Empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Empagliflozin

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when Empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with VORETA and VORETA PLUS .

Metformin

Hypoglycemia does not occur in patients receiving Metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as SUs and insulin) or ethanol.

Genital Mycotic Infections

Empagliflozin increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Monitor and treat as appropriate.

Increased Low-Density Lipoprotein Cholesterol (LDL-C)

Increases in LDL-C can occur with Empagliflozin. Monitor and treat as appropriate.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with VORETA and VORETA PLUS .

DOSAGE AND ADMINISTRATION

Recommended Dosage for VORETA

The recommended dose of VORETA is 10 mg once daily in the morning, taken with or without food.

In patients tolerating VORETA , the dose may be increased to 25 mg [In patients with volume depletion, correcting this condition prior to initiation of VORETA is recommended.

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue VORETA at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart VORETA if renal function is stable.

Recommended Dosage for VORETA PLUS

In patients with volume depletion not previously treated with Empagliflozin, correct this condition before initiating VORETA PLUS. Individualize the starting dose of VORETA PLUS based on the patient's current regimen. In patients on Metformin hydrochloride, switch to VORETA PLUS containing Empagliflozin 5 mg with a similar total daily dose of Metformin hydrochloride. In patients on Empagliflozin, switch to VORETA PLUS containing Metformin hydrochloride 500 mg with a similar total daily dose of Empagliflozin. In patients already treated with Empagliflozin and Metformin hydrochloride, switch to VORETA PLUS containing the same total daily doses of each component.

Take VORETA PLUS twice daily with meals; with gradual dose escalation to reduce the gastrointestinal side effects due to Metformin. Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of Metformin hydrochloride 2000 mg and Empagliflozin 25 mg.

Recommended Dosage in Patients with Renal Impairment

Assess renal function prior to initiation of VORETA and VORETA PLUS and periodically, thereafter. VORETA and VORETA PLUS are contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2.

OVERDOSAGE

Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of Empagliflozin by hemodialysis has not been studied. However, Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated Metformin from patients in whom VORETA and VORETA PLUS overdosage is suspected.

Overdose of Metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia is reported in approximately 10% of cases, but no causal association with Metformin has been established. Lactic acidosis has been reported in approximately 32% of Metformin overdose cases.

STORAGE/PRECAUTIONS: Store in a cool, dry and dark place between 15-30 ^{o}C. Keep all medicines out of the reach of children. To be used on the prescription of Registered Medical Practitioners.

PRESENTATION: VORETA Tablets 10mg, 25mg are available in packing containing 10 tablets.

VORETA PLUS Tablets 5/500 , 5/1000, 12.5/500 & 12.5/1000 mg are available in packing containing 10 tablets.

*Scotmann Specs.

خوراک: ڈاکٹر کی ہدایت کے مطابق۔

احتیاط: روشنی، نمی اور گرمی سے بچائیں۔ 15 سے 30 ڈگری سینٹی گریڈ کے درمیان محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

مستند ڈاکٹر کے نسخہ پر فروخت اور استعمال کریں۔

Complete Medical Information available only for doctors on request.

scotmann

Manufactured by: **SCOTMANN PHARMACEUTICALS**
5-D, I-10/3 Industrial Area, Islamabad-Pakistan.
www.scotmann.com