Dapaduo XR Tablets

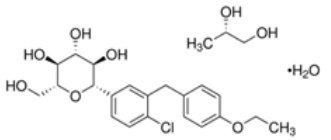
ڈیپاڈوایکس آر ٹیبلٹس

WARNING: LACTIC ACIDOSIS
·Postmarketing 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 DAPADUO XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

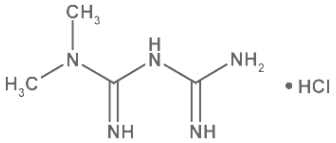
COMPOSITION:
Each film coated bi-layered tablet contains
Dapagliflozin (as propanediol monohydrate)
(Immediate release): 5 mg
Metformin hydrochloride
(Extended release): 500 mg
Each film coated bi-layered tablet contains
Dapagliflozin (as propanediol monohydrate)
(Immediate release): 5 mg
Metformin hydrochloride
(Extended release): 1000 mg
Each film coated bi-layered tablet contains
Dapagliflozin (as propanediol monohydrate)
(Immediate release): 10 mg
Metformin hydrochloride
(Extended release): 1000 mg

DESCRIPTION:
Dapaduo XR (dapagliflozin and metformin HCl extended-release) tablets contain two oral antihyperglycemic medications used in the management of type 2 diabetes: dapagliflozin and metformin hydrochloride.

Dapagliflozin:
Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4- ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1). The empirical formula is C21H25ClO6C3H8O2H2O and the formula weight is 502.98. The structural formula is:



Metformin hydrochloride:
Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide 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, slightly soluble in alcohol, 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:
Dapaduo XR
Dapaduo XR combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and metformin HCl, a biguanide.
Dapagliflozin
Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre- and afterload of the heart and downregulation of sympathetic activity.
Metformin HCl
Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both 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. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.
Pharmacodynamics:
General
Dapagliflozin Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin. Dapagliflozin doses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume. After discontinuation of dapagliflozin, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg dose.
Pharmacokinetics:
Dapaduo XR
The administration of Dapaduo XR in healthy subjects after a standard meal compared to the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin extended-release. Compared to the fasted state, the standard meal resulted in 35% reduction and a delay of 1 to 2 hours in the peak plasma concentrations of dapagliflozin. This effect of food is not considered to be clinically meaningful. Food has no relevant effect on the pharmacokinetics of metformin when administered as Dapaduo XR combination tablets.
Absorption
Dapagliflozin
Following oral administration of dapagliflozin, the maximum plasma concentration (Cmax) is usually attained within 2 hours under fasting state. The Cmax and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its Cmax by up to 50% and prolongs Tmax by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.
Metformin HCl
Following a single oral dose of metformin extended-release, Cmax is

achieved with a median value of 7 hours and a range of 4 to 8 hours. The extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food. There was no effect of food on Cmax and Tmax of metformin.

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Metformin HCl

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate release metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes.

Metabolism

Dapagliflozin

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [14C]-dapagliflozin dose and is the predominant drug-related component in human plasma.

Metformin HCl

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

ADVERSE REACTIONS:

The most common adverse reactions associated with Dapaduo XR (5% or greater incidence) were female genital mycotic infection, nasopharyngitis, urinary tract infection, diarrhea, and headache.

Adverse reactions reported in >5% of patients treated with metformin extended-release and more commonly than in patients treated with placebo are: diarrhea and nausea/vomiting.

WARNINGS AND PRECAUTIONS:

Lactic Acidosis: There have been post-marketing 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.

Hypotension: Before initiating Dapaduo XR, assess and correct volume status in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. ***Ketoacidosis:*** Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue Dapaduo XR, evaluate and treat promptly. Before initiating Dapaduo XR, consider risk factors for ketoacidosis. Patients on Dapaduo XR may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis.

Acute Kidney Injury: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy.

Urosepsis and Pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia: In patients taking insulin or an insulin secretagogue with Dapaduo XR, consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment.

Vitamin B12 Deficiency: Metformin may lower vitamin B12 levels. Measure hematological parameters annually.

Genital Mycotic Infections: Monitor and treat if indicated.

CONTRAINDICATIONS:

Severe renal impairment: (eGFR below 30 mL/min/1.73 m^2), end-stage renal disease or dialysis.

History of serious hypersensitivity to dapagliflozin or hypersensitivity to metformin HCl.

Metabolic acidosis, including diabetic ketoacidosis.

USE IN SPECIFIC POPULATIONS

Pregnancy: Advise females of the potential risk to a fetus, especially during the second and third trimesters.

Lactation: Dapaduo XR is not recommended when breastfeeding.

Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy.

Geriatrics: Higher incidence of adverse reactions related to reduced intravascular volume. Assess renal function more frequently.

Renal Impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function.

Hepatic Impairment: Avoid use in patients with hepatic impairment.

DOSAGE AND ADMINISTRATION:

- Assess renal function before initiating. Do not initiate or continue if eGFR is below 45 mL/min/1.73 m2.
- Individualize the starting dose based on the patient's current treatment.
- Administer once daily in the morning with food.
- Swallow whole. Never crush, cut, or chew.
- For patients not already taking dapagliflozin, the recommended starting dose for dapagliflozin is 5 mg once daily.
- The recommended dose of dapagliflozin to reduce the risk of hospitalization for heart failure is 10 mg once daily.
- For patients requiring a dose of 5 mg dapagliflozin and 2000 mg metformin HCl extended-release, use two of the 2.5 mg/1000 mg metformin HCl extended release tablets.
- Do not exceed a daily dose of 10 mg dapagliflozin/2000 mg metformin HCl extended-release.
- No dosage adjustment is indicated in patients with eGFR greater or equal to 45 mL/min/1.73 m^2.
- Dapaduo XR may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures.

PRECAUTIONS

Avoid direct sunlight and protect from moisture and heat. Store below 25°C. Keep all medicines out of the reach of children. To be sold and used on the prescription of Registered Medical Practitioners only.

PRESENTATION

DAPADUO XR 5/500 mg, 5/1000 mg & 10/1000 mg are available in packing containing 14 film coated bi-layered tablets, respectively.

عمومی خوراک: ڈاکٹر کی ہدایت کے مطابق۔

احتیاط: دھوپ، نمی اور گرمی سے بچائیں۔ 25 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔ مستند ڈاکٹر کے نسخہ پر فروخت اور استعمال کریں۔

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