HOSPIMAX
Maximising Life

Nefdapa™

Dapagliflozin 5 mg, 10 mg Tablets

Safe & Sustainable in Diabetes Management

Product Description: -

- **Nefdapa-5:** Each film coated tablet contains: Dapagliflozin 5mg
- **Nefdapa-10:** Each film coated tablet contains Dapagliflozin 10mg

General Information: -

Dapagliflozin is a sodium-glucose cotransporter 2 inhibitor indicated for managing diabetes mellitus type 2.When combined with diet and exercise in adults, dapagliflozin helps to improve glycaemic control by inhibiting glucose resorption in the proximal tubule of the nephron and causing glycosuria.Dapagliflozin was approved by the FDA on Jan 08, 2014.

Indication & Uses

Dapagliflozin is indicated to improve glycaemic control in adult patients with type 2 diabetes mellitus along with diet and exercise

Dosage & Administration

Type 2 diabetes mellitus

- The recommended starting dose is 5 mg once daily with or without food.
- Patients who required additional glycemic control the dose can be increased to 10 mg once daily.

Mechanism of action

Dapagliflozin is a highly potent selective and reversible inhibitor of SGLT2.
Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate inthe proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinaryexcretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium tothe distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure.

This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling andpreserve renal function.
Other effects include an increase in haematocrit and reduction in body weight.The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-loweringeffect and not limited to patients with diabetes

Pharmacokinetics

Absorption

Oral dapagliflozin reaches a maximum concentration within 1 hour of administration when patients have been fasting. When patients have consumed a high fat meal, the time to maximum concentration increases to 2 hours and the maximum concentration decreases by half though a dose adjustment is not necessary. Oral dapagliflozin is 78% bioavailable

Metabolism

Dapagliflozin is primarily glucuronidated to become the inactive 3-O-glucuronide metabolite(60.7%). Dapagliflozin also produces another minor glucuronidated metabolite (5.4%), a de-ethylated metabolite(<5%), and a hydroxylated metabolite(<5%)[1]. Metabolism of dapagliflozin is mediated by cytochrome p-450(CYP)1A1, CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP3A4, uridine diphosphate glucuronyltransferase(UGT)1A9, UGT2B4, and UGT2B7[2]. Glucuronidation to the major metabolite is mediated by UGT1A9

Route of elimination

75.2% of dapagliflozin is recovered in the urine with 1.6% of the dose unchanged by metabolism. 21% of the dose is excreted in the feces with 15% of the dose unchanged by metabolism

Pregnancy: There are no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, the use of dapagliflozin is not recommended during thesecond and third trimesters of pregnancy.When pregnancy is detected, treatment with dapagliflozin should be discontinued.
Breast-feeding:
It is unknown whether dapagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring. A risk tothe newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.
Paediatric population: The safety and efficacy of dapagliflozin in children aged 0 to < 18 years have not yet been established.
Elderly (≥ 65 years): No dose adjustment is recommended based on age.

Dapagliflozin is not recommended in patients with a creatinine clearance below 45mL/min and is contraindicated in patients with creatinine clearance below 30mL/min. Dose adjustments are not necessary in patients with hepatic impairment at any stage, although the risk and benefit to the patient must be assessed as there is limited data on dapagliflozin use in this population

Food Interactions

- Avoid excessive or chronic alcohol consumption. Binge drinking or drinking alcohol often may predispose patients to ketoacidosis.
- Take with or without food

Drug Interaction

Diuretics

Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension

Insulin and insulin secretagogues

Lowerdose of insulin or an insulin secretagoguesuch as sulphonylureas,may be required to reduce the risk of hypoglycaemia whenused in combination with dapagliflozin in patients with type 2 diabetes mellitus

Rifampicin: With rifampicin (an inducer of various active transportersand drug-metabolising enzymes) a 22% decrease in dapagliflozin systemic exposure (AUC) wasobserved, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No doseadjustment is recommended.

Following coadministration of dapagliflozin with **mefenamic acid** (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended

Dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

Adverse Effects:

Very Common: Hypoglycaemia(when used with Sulfonylurea or insulin)

Common(≥ 2% of subjects)**:** Vulvovaginitis, balanitis and related genital infections, Urinary tract infection, Dizziness, Rash, Back pain, Dysuria, Polyuria, Haematocrit, increased, Creatinine renal clearance decreased during initial treatment Dyslipidaemia

Uncommon (≥ 0.2% of subjects)**:** Fungal infection, Volume depletion Thirst, Constipation Dry mouth, Nocturia, Vulvovaginal pruritus, Pruritus genital, Blood creatinine increased during initial treatment, Blood urea increased, Weight decreased

Rare: Diabetic ketoacidosis (when used in type 2 diabetes mellitus)

Very rare: Necrotising fasciitis of the perineum (Fournier's gangrene), Angioedema

Warnings & Precautions

- **Volume depletion**: Before initiating dapagliflozin, assess volume status and renal function in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy.
- **Ketoacidosisin Patients with Diabetes Mellitus**: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue dapagliflozin, evaluate and treat promptly. Before initiating dapagliflozin, consider risk factors for ketoacidosis. Patients on dapagliflozin may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis.
- **Urosepsis and Pyelonephritis**: Evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated.
- **Hypoglycaemia:** Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycaemia when used in combination with dapagliflozin.
- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Serious, life-threatening cases have occurred in patients with diabetes, 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.

- **Genital Mycotic Infections:** Monitor and treat if indicated