FOR THE USE ONLY OF A REGISTERED MEDICAL PRACTITIONER OR A HOSPITAL OR A LABORATORY

DAPAGLIFLOZIN AND METFORMIN HYDROCHLORIDE EXTENDED RELEASE TABLETS 5 MG/1000 MG

ZINODAP® M-5/1000

DAPAGLIFLOZIN AND METFORMIN HYDROCHLORIDE EXTENDED RELEASE TABLETS 10 MG/500 MG

ZINODAP® M-10/500

DAPAGLIFLOZIN AND METFORMIN HYDROCHLORIDE EXTENDED RELEASE TABLETS 10 MG/1000 MG

ZINODAP® M-10/1000

WOCKHARDT

1. GENERIC NAME
Dapagliflozin and Metformin Hydrochloride Extended Release tablets 5mg/1000mg, 10mg/500mg & 10mg/ 1000mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
ZINODAP M 5/1000
Each Film Coated Tablet Contains
Dapagliflozin propanediol monohydrate eq. to
Dapagliflozin…..5mg
Metformin Hydrochloride I.P. ... 1000 mg
Extended release
Excipients.. q.s.
Colour: Ferric oxide Red USP-NF & Titanium Dioxide IP

ZINODAP M 10/500
Each Film Coated Tablet Contains
Dapagliflozin propanediol monohydrate eq. to
Dapagliflozin 10mg
Metformin Hydrochloride I.P. ... 500 mg
Extended release
Excipients.. q.s.
Colour: Ferric oxide Yellow USP-NF & Titanium Dioxide IP

ZINODAP M 10/1000
Each Film Coated Tablet Contains
Dapagliflozin propanediol monohydrate eq. to
Dapagliflozin 10mg
Metformin Hydrochloride I.P. ... 1000 mg
Extended release
Excipients.. q.s.
Colour: Ferric oxide Yellow USP-NF & Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH
Dosage Form: Film coated Tablets for oral use
Strength :
Dapagliflozin 5 mg and Metformin Hydrochloride (extended release) 1000mg
Dapagliflozin 10 mg and Metformin Hydrochloride (extended release) 500mg
Dapagliflozin 10 mg and Metformin Hydrochloride (extended release) 1000mg

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
ZINODAP M is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both Dapagliflozin and Metformin is appropriate.

Dapagliflozin is indicated to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.

Limitations of use
ZINODAP M is not recommended for patients with type I diabetes mellitus or for the treatment of diabetic ketoacidosis.

4.2. Posology and Method of Administration

Prior to Initiation of ZINODAP M
Assess renal function prior to initiation of Zinodap M and periodically thereafter.
In patients with volume depletion, correct this condition prior to initiation of Zinodap M.

Recommended Dosage
Zinodap M should be taken once daily in the morning with food with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin. Tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of Zinodap M will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet. Individualize the starting dose of Zinodap M based upon the patient's current regimen. For patients not already taking dapagliflozin, the recommended starting dose for dapagliflozin is 5 mg once daily. To reduce the risk of hospitalization for heart failure, the recommended dose for dapagliflozin is 10 mg once daily. Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 10 mg dapagliflozin and 2000 mg metformin.

Patients with Renal Impairment
No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2
Zinodap M is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2. Zinodap M is not recommended in patients with an eGFR below 45 mL/min/1.73 m^2

Discontinuation for Iodinated Contrast Imaging Procedures
Discontinue Zinodap M at the time of, or prior to, an iodinated contrast imaging procedure 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 Zinodap M if renal function is stable.

4.3. Contraindications
Zinodap M is contraindicated in patients with:
Severe renal impairment (eGFR below 30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis.
History of a serious hypersensitivity reaction to dapagliflozin or hypersensitivity to metformin hydrochloride.
Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

4.4. Special Warnings and precautions for use

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. 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 Zinodap M.
In Zinodap M 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.
Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue Zinodap M and report these symptoms to their healthcare provider.

Hypotension
Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating dapagliflozin particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics. Before initiating Zinodap M in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy

Ketoacidosis
Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin. Zinodap M is not indicated for the treatment of patient with type 1 diabetes mellitus.

Patients treated with Zinodap M who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose as ketoacidosis associated with Zinodap M may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Zinodap M should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement

In patients with type I diabetes, the presence of ketoacidosis was not immediately recognized, and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 m/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis, such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type I diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating Zinodap M, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing Zinodap M for at least 3 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing Zinodap M in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting Zinodap M

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Zinodap M and seek medical attention immediately if signs and symptoms occur.

Acute Kidney Injury
Dapagliflozin causes intravascular volume contraction and can cause acute kidney injury.
There have been post marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving dapagliflozin.

Increases in serum creatinine and decreases in estimated GFR may also be observed with initiation of dapagliflozin. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Before initiating dapagliflozin consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing dapagliflozin in the setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury.

If acute kidney injury occurs, discontinue Zinodap M promptly and institute treatment.
Renal function should be evaluated prior to initiation of Zinodap M and monitored periodically thereafter. Use of Zinodap M is not recommended when the eGFR is less than 45 mL/min/1.73 m^2. Zinodap M is contraindicated in patients with an eGFR below 30 mL/min/1.73 m^2

Urosepsis and Pyelonephritis
There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including Dapagliflozin. 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

Insulin and insulin secretagogues are known to cause hypoglycemia. Zinodap M may increase the risk of hypoglycemia when combined with insulin or insulin secretagogues. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with Zinodap M.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life threatening necrotizing infection requiring urgent surgical intervention, have been identified in post-marketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. Both males and females have been equally affected. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with Zinodap M presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue Zinodap M, closely monitor blood glucose levels, and provide appropriate alternative therapy of glycemia control.

Genital Mycotic Infections
Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat appropriately.

Lower limb amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

Vitamin B12 Concentrations
In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. This decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measurement of hematologic parameters on an annual basis is advised in patients on Zinodap M and any apparent abnormalities should be appropriately investigated and managed.
Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at 2 to 3 year intervals may be useful.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C)
Increases in LDL-C occur with dapagliflozin. Monitor LDL-C and treat per standard of care after initiating Zinodap M.

Bladder Cancer
There are insufficient data to determine whether dapagliflozin has an effect on pre-existing bladder tumors. Consequently, Zinodap M should not be used in patients with active bladder cancer. In patients with prior history of bladder cancer, the benefits of glycemic control versus unknown risks for cancer recurrence with Zinodap M should be considered.

4.5. Drug Interactions

Dapagliflozin

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 glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Pharmacodynamic interactions
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
Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with dapagliflozin in patients with type 2 diabetes mellitus

Pharmacokinetic interactions
The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT 1 A9).
Dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2CS, CYP2C9, CYP2CI9, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore dapagliflozin is not expected to alter the metabolic clearance of co-administered medicinal products that are metabolised by these enzymes.

Effect of other medicinal products on Dapagliflozin
Pharmacokinetics of dapagliflozin is not altered by metformin, pioglitazone, sitagliptin, glimepride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug metabolising enzymes) a 22% decrease in dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g. carbamazepine, phenytoin, phenobarbital) is not expected.

Following coadministration of dapagliflozin with mefenamic acid (an inhibitor ofUGT1A9), 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.

Effect of dapagliflozin on other medicinal products
Dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimipride. Hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of 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.

Metformin hydrochloride
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 Zinodap M may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.
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.
Alcohol
Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Zinodap M.
Use with Other Drugs
Some medications can predispose to hyperglycemia and may lead to loss of glycemic control. These medications 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 Zinodap M, the patient should be observed closely for loss of glycemic control. When such drugs are withdrawn from a patient receiving Zinodap M, the patient should be observed closely for hypoglycemia. In healthy volunteers, the pharmacokinetics of metformin and propranolol, and of metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy
There are no adequate and well-controlled studies of Zinodap M or its individual components in pregnant women. Dapagliflozin is not recommended during the second and third trimesters of pregnancy. Limited data with dapagliflozin in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. Zinodap M should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose.

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with an HbA1c greater than 7% and has been reported to be as high as 20 to 25% in women with HbA1c greater than 10%. The estimated background risk of miscarriage for the indicated population is unknown.

Disease-associated maternal and/or embryo fetal risk
Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity

Data
Human Data
Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.
Animal Data
Dapagliflozin
Dapagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and increased the incidence of renal pelvic and tubular dilatations at all dose levels. Exposure at the lowest dose tested was 15-times the 10 mg clinical dose (based on AUC). The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.
In a prenatal and postnatal development study, dapagliflozin was administered to maternal rats from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed in utero and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in 21-day-old pups offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415-times and 137-times, respectively, the human values at the 10 mg clinical dose, based on AUC). Dose-related reductions in pup body weights were observed at greater or equal to 29-times the 10 mg clinical dose (based on AUC). No adverse effects on developmental endpoints were noted at 1 mg/kg/day (19-times the 10 mg clinical dose, based on AUC). These outcomes occurred with drug exposure during periods of renal development in rats that corresponds to the late second and third trimester of human development.
In embryofetal development studies in rats and rabbits, dapagliflozin was administered throughout organogenesis, corresponding to the first trimester of human pregnancy. In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day (1441-times the 10 mg clinical dose, based on AUC). Dose related effects on the rat fetus (structural abnormalities and reduced body weight) occurred only at higher dosages, equal to or greater than 150 mg/kg (more than 2344-times the 10 mg clinical dose, based on AUC), which were associated with maternal toxicity. No developmental toxicities were observed in rabbits at doses up to 180 mg/kg/day (1191-times the 10 mg clinical dose, based on AUC).
Metformin HCl
Metformin HCl did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about 2-and 6-times a 2000 mg clinical dose based on body surface area (mg/m2) for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Lactation
It is not known whether Zinodap M or Dapagliflozin is excreted in human milk. Limited published studies report that metformin is present in human milk. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. In studies performed with the individual components, both dapagliflozin (reaching levels 0.49 times that found in maternal plasma) and metformin are excreted in the milk of lactating rats. Because of the potential for serious adverse reactions in breastfed infants, advise women that use of Zinodap M is not recommended while breastfeeding.
Data in juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and in the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from dapagliflozin, a decision should be made whether to discontinue nursing or to discontinue Zinodap M, taking into account the importance of the drug to the mother.

Data
Dapagliflozin
Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49, indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.
Metformin HCl
Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

Females and Males of Reproductive Potential
Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

Pediatric Use
Safety and effectiveness of Zinodap M in pediatric patients under 18 years of age has not been established.

Geriatric Use
No dosage change is recommended based on age. More frequent assessment of renal function is recommended in elderly patients.
After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients≥65 years of age, a higher proportion of patients treated with dapagliflozin had adverse reactions of hypotension.
Metformin is known to be substantially excreted by the kidney and because the risk of lactic acidosis with metformin is greater in patients with moderately to severely impaired renal function. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients.

Renal Impairment
Use of dapagliflozin is not recommended when eGFR is less than 45 mL/min/1.73 m^2 and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or ESRD. Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Zinodap M is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2

Patients with renal impairment using dapagliflozin for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury. Patients with an eGFR 30 to less than 60 mL/min/1.73m^2, receiving Dapagliflozin experienced bone fractures.

Hepatic Impairment
Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Zinodap M is not recommended in patients with hepatic impairment.

4.7. Effects on Ability to Drive and Use Machines
Zinodap M has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

4.8. Undesirable Effects

Dapagliflozin
- Hypotension
- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Genital Mycotic Infections

Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

System organ class	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections Urinary tract infection	Fungal infection		Necrotising fasciitis of the perineum (Fournier's gangrene)
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)		Volume depletion Thirst	Diabetic ketoacidosis	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation Dry mouth		
Skin and subcutaneous tissue disorders		Rash			Angioedema
Musculoskeletal and connective tissue disorders		Back pain			
Renal and urinary disorders		Dysuria Polyuria	Nocturia		
Reproductive system and breast disorders			Vulvovaginal pruritus Pruritus genital		
Investigations		Haematocrit increased Creatinine renal clearance decreased during initial treatment Dyslipidaemia	Blood creatinine increased during initial treatment Blood urea increased Weight decreased		

Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.

Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolemia and hypotension.

Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

Metformin
In placebo-controlled monotherapy trials of metformin extended-release, diarrhea and nausea/vomiting were reported in >5% of metformin-treated patients and more commonly than in placebo-treated patients (9.6% versus 2.6% for diarrhea and 6.5% versus 1.5% for nausea/vomiting). Diarrhea led to discontinuation in 0.6% of the patients treated with metformin extended-release. Cholestatic, hepatocellular, and mixed hepatocellular liver injury were additional adverse reactions identified.
Dapagliflozin and Metformin
- Female genital mycotic infections
- Nasopharyngitis
- Urinary tract infections
- Diarrhea
- Headache
- Male genital mycotic infections
- Influenza
- Nausea
- Back pain
- Dizziness
- Cough
- Constipation
- Dyslipidemia
- Pharyngitis
- Increased urination
- Discomfort with urination

No additional adverse reactions were identified for the dapagliflozin plus metformin group compared with those reported for the individual components. In studies with dapagliflozin in add-on combination with metformin, minor episodes of hypoglycaemia were reported at similar frequencies in the group treated with dapagliflozin 10 mg plus metformin (6.9%) and in the placebo plus metformin group (5.5%). No major events of hypoglycaemia were reported. Similar observations were made for the combination of dapagliflozin with metformin in drug-naive patients.
Laboratory test
Increases in Serum Creatinine and Decreases in eGFR
Initiation of dapagliflozin causes an increase in serum creatinine and decrease in eGFR.
In patients with normal or mildly impaired renal function at baseline, serum creatinine and eGFR returned to baseline at Week 24. Sustained decreases in eGFR were seen in patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73m^2)

Increase in Serum Inorganic Phosphorus
Increases from baseline in mean serum phosphorus levels were observed in dapagliflozin-treated patients

Increase in Hematocrit
Increases from baseline in mean hematocrit values were observed in dapagliflozin-treated patients.

Increase in Low-Density lipoprotein Cholesterol
Changes from baseline in mean lipid values were reported in dapagliflozin-treated patients.

Decrease in Serum Bicarbonate
Concomitant therapy of dapagliflozin with exenatide extended-release resulted in serum bicarbonate value of less than or equal to 13 mEq/L.

Vitamin B12 Concentrations
Metformin may lower serum vitamin B12 concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on Zinodap M and any apparent abnormalities should be appropriately investigated and managed.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important; it allows continued monitoring of the benefit/risk balance of the medicinal product.
If you experience any side effects, talk to your doctor or write to us at "PVSafety@wockhardt.com". You can also report side effects by calling Wockhardt Pharmacovigilance at +91-22-26596776 (All working days 9:00 AM to 5:00PM) or directly to Pharmacovigilance Program of India (PvPI) helpline 1800-180-3024 (All working days 9:00 AM to 5:30PM)."

4.9. Overdose

Dapagliflozin
In the event of overdose employ supportive measures as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.
Metformin hydrochloride
Overdose of metformin hydrochloride has occurred, including ingestion of amounts >50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Zinodap M 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 hydrochloride, 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 down regulation of sympathetic activity.
Metformin hydrochloride
Metformin improves glucose tolerance in patients with type 2 diabetes, 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. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or in healthy subjects, except in unusual 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.

5.2 Pharmacodynamic Properties
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 at Week 12. 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.

Cardiac Electrophysiology
Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15-times the recommended maximum dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses up to 500 mg (50-times the recommended maximum dose) of dapagliflozin in healthy subjects.

5.3 PHARMACOKINETIC PROPERTIES

Absorption
Dapagliflozin
Following oral administration of dapagliflozin, the maximum plasma concentration (Cmax) is usually attained within 2 hours under fasting state. [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 10mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs Tmax, by approximately 1 hour, but does not alter AUC as compared with the fasted state. Dapagliflozin can be administered with or without food.

Metformin hydrochloride
Following a single oral dose of metformin sustained-release, C_{max} 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 sustained-release tablet increased by approximately 50% when given with food. There was no effect of food on C_{max} and T_{max} of metformin.

Distribution
Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.
Metformin hydrochloride
Distribution studies with sustained-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 UGTIA9; 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 hydrochloride
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. Metabolism studies with sustained-release metformin tablets have not been conducted

Elimination
Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50mg dose of [14C] dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal halflife ($t_{1/2}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of Dapagliflozin 10 mg.
Metformin hydrochloride
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.

Specific Populations
Renal impairment

Dapagliflozin
At steady-state (20 mg once daily dapagliflozin for 7 days), patients with type 2 diabetes with mild, moderate, or severe renal impairment (as determined by eGFR) had geometric mean systemic exposures of dapagliflozin that were 45%, 2.04-fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes with normal renal function. Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment did not result in a correspondingly higher 24-hour urinary glucose excretion.

The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than patients with type 2 diabetes with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known.
Metformin hydrochloride
In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased
Hepatic Impairment
Dapagliflozin
In case of mild and moderate hepatic impairment (Child-Pugh classes A and B), mean and AUC of dapagliflozin were up to 12% and 36% higher. These differences were not considered to be clinically meaningful. In patients with severe hepatic impairment (Child-Pugh class C), mean Cmax and AUC of dapagliflozin were up to 40% and 67% higher, respectively.

Metformin hydrochloride
No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Effects of Age, Gender, Race, and Body Weight on pharmacokinetics

Dapagliflozin
Based on a population pharmacokinetic analysis, age, gender, race, and body weight do not have a clinically meaningful effect on the pharmacokinetics of dapagliflozin and thus, no dose adjustment is recommended.
Metformin hydrochloride
Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.
Metformin pharmacokinetic parameters did not differ significantly between healthy subjects and patients with type 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.
No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

Pediatric

Pharmacokinetics in the pediatric population has not been studied

Drug Interactions
Specific pharmacokinetic drug interaction studies with Zinodap M have not been performed, although such studies have been conducted with the individual dapagliflozin and metformin components.
In Vitro Assessment of Drug Interactions
In in vitro studies, dapagliflozin and dapagliflozin 3-0-glucuronide neither inhibited CYP1A2, 2C9, 2C19, 2D6, or 3A4, nor induced CYP 1A2, 2B6 or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter, and dapagliflozin 3-0-glucuronide ¡s a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-0-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT I, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT 1, or OAT3 substrates.

Effects of Other Drugs on Dapagliflozin
No dose adjustments are recommended for dapagliflozin.

Effects of Dapagliflozin on Other Drugs
Dapagliflozin did not meaningfully affect the pharmacokinetics of the coadministered drugs

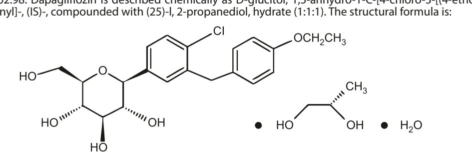
6. NONCLINICAL PROPERTIES
6.1 Animal Toxicology or Pharmacology
No animal studies have been conducted with Zinodap M to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findings in the studies with dapagliflozin and metformin individually.
Dapagliflozin
Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were approximately 72-times (males) and 105-times (females) the clinical dose of 10 mg per day, based on AUC exposure. In rats, the highest dose was approximately 131-times (males) and 186-times (females) the clinical dose of 10 mg per day, based on AUC exposure.

Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of in vitro clastogenicity assays in the presence of S9 activation and at concentrations greater than or equal to 100 mcg/ml. Dapagliflozin was negative for clastogenicity in a series of in vivo studies evaluating micronuclei or DNA repair in rats at exposure multiples greater than 2100-times the clinical dose.

There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans.

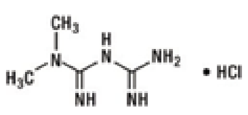
Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at exposure multiples less than or equal to 1708-times and 998-times the maximum recommended human dose in males and females, respectively.
Metformin hydrochloride
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the MRHD of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day. There was no evidence of a mutagenic potential of metformin in the following in vitro tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative. Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human dose based on body surface area comparisons.

7. DESCRIPTION
Zinodap M (dapagliflozin and metformin HCl extended release) tablets contain two oral antihyperglycemic medications used in the management of type 2 diabetes: dapagliflozin and metformin hydrochloride (ER).
Dapagliflozin
Dapagliflozin belongs to the chemical class of sodium-glucose co-transporter 2 (SGLT2) inhibitors. It is available as film-coated tablets containing 5 mg and 10 mg. It has a molecular formula of $C_{21}H_{25}ClO_2.C_3H_8O_2.H2O$ and a molecular weight of 502.98. Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl]-, (IS)-, compounded with (25)-l, 2-propanediol, hydrate (1:1:1). The structural formula is:



Dapagliflozin is available as off-while amorphous powder. Dapagliflozin is soluble in methanol and is insoluble in cyclohexane, water, pH 1.2 solution (hydrochloric acid buffer), pH 3 (solution acid phthalate buffer), pH 4.5 solution (acetate buffer), phosphate buffer (pH 6.8, 7.2, 8.0), 0.1N HCL.

Metformin hydrochloride
Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula of C4H11N5•HCl 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:



8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities
None

8.2 Shelf-life
24 months

8.3 Packing Information
Alu-Alu Blister pack

8.4 Storage and Handling Instructions
Store below 30°C away from direct sunlight, heat and moisture

9. PATIENT COUNSELING INFORMATION
Advise the patient to read package insert.

Hypotension
Inform patients that symptomatic hypotension may occur with dapagliflozin and advise them to contact their healthcare provider if they experience such symptoms. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Hypoglycemia
Inform patients that hypoglycemia can occur particularly, when co-administered with insulin formulation. In order to reduce the risk of hypoglycemia, advise patients to decrease the quantity these drugs when given in combination with insulin. Instruct patients on self-management procedures including glucose monitoring, and management of hypoglycemia and hyperglycemia. Instruct patients on handling of special situations such as illness, stress, or emotional disturbances, an inadequate or skipped dose, inadvertent administration of an increased dose, inadequate food intake, and skipped meals,
Instruct patients on the management of hypoglycemia. Advise patients to regularly carry some sugar lumps, sweets, biscuits, or sugary fruit juice to mitigate symptoms of hypoglycemia. Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery. [see Special warnings and precautions for use(4.4)].
Hypoglycemia due to Medication Errors
Instruct patients that hypoglycemia may occur as a result of overdose; relative to food intake, energy expenditure, or both.

Ketoacidosis
Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of dapagliflozin, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated.
If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness and laboured breathing) occur, instruct patients to discontinue dapagliflozin and seek medical attention immediately.

Acute Kidney Injury
Inform patients that acute kidney injury has been reported during use of dapagliflozin. Advise patients to seek medical advice immediately if they have reduced oral intake (due to acute illness or fasting) or increased fluid losses (due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue Dapagliflozin use in those settings.

Serious Urinary Tract Infections
Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice promptly if such symptoms occur.

Necrotizing Fasciitis of the Perineum (Fournier 's Gangrene)
Inform patients that necrotizing infections of the perineum (Fournier's Gangrene) have occurred with Dapagliflozin. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise.

Genital Mycotic Infections in Females (e.g. Vulvovaginitis)
Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice.

Genital Mycotic Infections in Males (e.g., Balanitis)
Inform male patients that yeast infections of the penis (e.g., balanitis or balanoposthitis) may occur, especially in patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice.

Hypersensitivity Reactions
Inform patients that serious hypersensitivity reactions (e.g., urticaria, anaphylactic reactions, and angioedema) have been reported with Dapagliflozin. Advise patients to immediately report any signs or symptoms suggesting allergic reaction or angioedema, and to take no more of the drug until they have consulted prescribing physicians.

Vitamin B12 concentration
Advise patients on Zinodap M to measure hematologic parameters on an annual basis and any apparent abnormalities should be appropriately investigated and managed.
Pregnancy
Advise pregnant patients of the potential risk to a fetus with treatment with Dapagliflozin.
Instruct patients to immediately inform their healthcare provider if pregnant or planning to become pregnant.

Lactation
Advise patients that use of Dapagliflozin is not recommended while breastfeeding.

Renal and Hepatic Impairment
Advise the patients that careful monitoring is required in renal impairment patients and Zinodap M is contraindicated in patients with moderate to severe renal impairment (eGFR less than 60 mL/min/1.73m2), ESRD or patients on dialysis. Advise the patients with renal impairment using dapagliflozin may also be more likely to experience hypotension and may be at higher risk for acute kidney injury.

Hepatic Impairment
Advise patients to avoid use of Zinodap M with clinical or laboratory evidence of hepatic disease as metformin been associated with some cases of lactic acidosis.
Storage and Handling
Instruct the patient that Zinodap M tablet should be stored temperature not exceeding 30°C away from direct sunlight, heat and moisture.

Laboratory Tests
Due to its mechanism of action, patients taking Dapagliflozin will test positive for glucose in their urine.

Missed Dose
If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses at the same time.

10. DETAILS OF MANUFACTURER
Exemed Pharmaceuticals,
Plot no.133/1 & 133/2, G.I.D.C., Selvas Road,
Vapi-396 195 Dist.: Valsad,
INDIA

11. MARKETED BY
Wockhardt Limited.
Wockhardt Towers, Bandra – Kurla Complex, Mumbai - 400051

12. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
G/25/2011 Dated: 12 Jul 2018

13. DATE OF REVISION:
24 May 2021

L.I.No.: m-6200

Front

Back

Size: 170 x 390 mm
Folded Size: 170 x 33 mm
K 100