For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

Rx

Pioglitazone Hydrochloride, Metformin Hydrochloride (ER) Tablets (15 mg + 1000 mg)

Mopaday® Forte

15mg / 1000mg

Advice for healthcare professionals:
- Patients with active bladder cancer or with a history of bladder cancer, and those with uninvestigated haematuria, should not receive pioglitazone
- Prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated. Pioglitazone should be stopped in patients who do not respond adequately to treatment (eg, reduction in glycosylated haemoglobin, HbA1c)
- Before starting pioglitazone, the following known risk factors for development of bladder cancer should be assessed in individuals: age; current or past history of smoking; exposure to some occupational or chemotherapy agents such as cyclophosphamide; or previous irradiation of the pelvic region
- Use in elderly patients should be considered carefully before and during treatment because the risk of bladder cancer increases with age. Elderly patients should start on the lowest possible dose and be regularly monitored because of the risks of bladder cancer and heart failure associated with pioglitazone.

WOCKHARDT

1. Generic Name
Pioglitazone hydrochloride, Metformin hydrochloride (ER) tablets (15 mg + 1000 mg)

2. Qualitative and quantitative composition
Each uncoated bi-layered tablet contains
Pioglitazone hydrochloride IP equivalent to Pioglitazone..... 15 mg
Metformin hydrochloride IP (in extended release form) ..... 1000 mg

3. Dosage form and strength
Uncoated bi-layered tablet. Pioglitazone hydrochloride, Metformin hydrochloride (ER) tablets (15 mg + 1000 mg)

4. Clinical particulars
4.1 Therapeutic indication
Mopaday forte is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both pioglitazone and metformin is appropriate as second line therapy.

4.2 Posology and method of administration
DOSAGE

Recommendations for All Patients
Mopaday Forte should be taken with meals to reduce the gastrointestinal side effects associated with metformin. Individualize the starting dose based on the patient's current regimen and adjust the dosing based on effectiveness and tolerability.

If therapy with a combination tablet containing pioglitazone and extended-release metformin is considered appropriate the recommended starting dose is:

- Mopaday Forte 15 mg/1000 mg once daily and gradually titrated as needed, after assessing adequacy of therapeutic response and tolerability.
- for patients with NYHA Class I or Class II congestive heart failure: 15 mg/1000 mg once daily and gradually titrated as needed, after assessing adequacy of therapeutic response and tolerability.
- for patients inadequately controlled on metformin monotherapy: 15 mg/1000 mg twice daily (depending on the dose of metformin already being taken) and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability.
- for patients inadequately controlled on pioglitazone monotherapy: 15 mg/1000 mg twice daily and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability.
- for patients who are changing from combination therapy of pioglitazone plus metformin as separate tablets: Mopaday Forte should be taken at doses that are as close as possible to the dose of pioglitazone and metformin already being taken

Mopaday Forte may be titrated up to a maximum daily dose of 45 mg/2000 mg of pioglitazone/extended-release metformin. Metformin doses above 2000 mg may be better tolerated given three times a day.

Patients should be informed that Mopaday Forte must be swallowed whole and not chewed, cut, or crushed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

Monitor patients for adverse events related to fluid retention such as weight gain, edema, and signs and symptoms of congestive heart failure after initiation and dose increases.
Obtain liver tests (serum alanine and aspartate aminotransferases, alkaline phosphatase, and total bilirubin) before initiation. Routine periodic monitoring of liver tests during treatment with Mopaday Forte is not recommended in patients without liver disease. If abnormal, use caution when treating with MOPADAY FORTE, investigate the probable cause, treat (if possible), and follow appropriately.

Recommendations for Use in Renal Impairment
Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR).
Do not use MOPADAY FORTE in patients with eGFR below 30 mL/min/1.73 m2
Initiation of MOPADAY FORTE is not recommended in patients with eGFR between 30 – 45 mL/min/1.73 m2
Assess risk/benefit of continuing MOPADAY FORTE if eGFR falls below 45 mL/min/1.73 m2
Discontinue MOPADAY FORTE if eGFR later falls below 30 mL/min/1.73 m2

Discontinuation for Iodinated Contrast Imaging Procedures
MOPADAY FORTE should be discontinued at time of, or prior to, iodinated contrast imaging procedures in patients with an eGFR between 30- 60 mL/min/1.73 m2 ; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intraarterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart MOPADAY FORTE if renal function is stable.

4.3 Contraindications
- Initiation in patients with established NYHA Class III or IV heart failure
- Severe renal impairment (eGFR below 30 mL/min/1.73 m2
- Use in patients with known hypersensitivity to pioglitazone, metformin, or any other component of MOPADAY FORTE.
- Metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.

4.4 Special warnings and precautions for use
Congestive Heart Failure
Pioglitazone, like other thiazolidinediones, can cause dose-related fluid retention when used alone or in combination with other antidiabetic medications and is most common when pioglitazone is used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure. Patients treated with MOPADAY FORTE should be observed for signs and symptoms of congestive heart failure. If congestive heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of MOPADAY FORTE must be considered.

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 (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels generally greater than 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 MOPADAY FORTE. In MOPADAY FORTE -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/min 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 MOPADAY FORTE and report these symptoms to their healthcare provider.

Edema
Edema was reported more frequently in patients treated with pioglitazone than in placebo-treated patients and is dose related. MOPADAY FORTE should be used with caution in patients with edema. Because thiazolidinediones, including pioglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, MOPADAY FORTE should be used with caution in patients at risk for congestive heart failure. Patients treated with MOPADAY FORTE should be monitored for signs and symptoms of congestive heart failure.

Hypoglycemia
Patients receiving MOPADAY FORTE in combination with insulin or other antidiabetic medications (particularly insulin secretagogues such as sulfonylureas) may be at risk for hypoglycemia. A reduction in the dose of the concomitant antidiabetic medication may be necessary to reduce the risk of hypoglycemia. Hypoglycemia can also occur when caloric intake is deficient or when strenuous exercise is not compensated by caloric supplement. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Hepatic Effects
There have been postmarketing reports of fatal and nonfatal hepatic failure in patients taking pioglitazone, although the reports contain insufficient information necessary to establish the probable cause. There has been no evidence of drug-induced hepatotoxicity in the pioglitazone controlled clinical trial database to date. Patients with type 2 diabetes may have fatty liver disease or cardiac disease with episodic congestive heart failure, both of which may cause liver test abnormalities, and they may also have other forms of liver disease, many of which can be treated or managed. Therefore, obtaining a liver test panel and assessing the patient is recommended before initiating MOPADAY FORTE therapy. In patients with abnormal liver tests, MOPADAY FORTE should be initiated with caution.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), MOPADAY FORTE treatment should be interrupted and investigation done to establish the probable cause. MOPADAY FORTE should not be restarted in these patients without another explanation for the liver test abnormalities. Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury, and should not be restarted on MOPADAY FORTE. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with MOPADAY FORTE can be used with caution.

Urinary Bladder Tumors
Pioglitazone may be associated with an increase in the risk of urinary bladder tumors. There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder tumors.
Consequently, MOPADAY FORTE should not be used in patients with active bladder cancer and the benefits of glycemic control versus unknown risks for cancer recurrence with MOPADAY FORTE should be considered in patients with a prior history of bladder cancer.

Fractures
The risk of fracture should be considered in the care of patients, especially female patients, treated with MOPADAY FORTE and attention should be given to assessing and maintaining bone health according to current standards of care.

Macular Edema
Macular edema has been reported in postmarketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione.

Vitamin B12 Levels
Measurement of hematologic parameters on an annual basis is advised in patients on MOPADAY FORTE 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 two-to three-year intervals may be useful.

4.5 Drugs interactions
Strong CYP2C8 Inhibitors
An inhibitor of CYP2C8 (e.g., gemfibrozil) significantly increases the exposure (area under the serum concentration-time curve or AUC) and half-life (t1/2) of pioglitazone. Therefore, the maximum recommended dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors

CYP2C8 Inducers
An inducer of CYP2C8 (e.g., rifampin) may significantly decrease the exposure (AUC) of pioglitazone. Therefore, if an inducer of CYP2C8 is started or stopped during treatment with pioglitazone, changes in diabetes treatment may be needed based on clinical response without exceeding the maximum recommended daily dose of 45 mg for pioglitazone

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 MOPADAY FORTE may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

Drugs that Reduce Metformin Clearance
Drugs that are eliminated by renal tubular secretion (e.g., cationic drugs such as cimetidine) have the potential for interaction with metformin by competing for common renal tubular transport systems, and may increase the accumulation of metformin and the risk for lactic acidosis.

Alcohol
Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving MOPADAY FORTE

Insulin Secretagogues or Insulin
If hypoglycemia occurs in a patient coadministered MOPADAY FORTE and an insulin secretagogue (e.g., sulfonylurea), the dose of the insulin secretagogue should be reduced. If hypoglycemia occurs in a patient coadministered MOPADAY FORTE and insulin, the dose of insulin should be decreased by 10% to 25%. Further adjustments to the insulin dose should be individualized based on glycemic response.

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 blockers, and isoniazid. When such drugs are administered to a patient receiving MOPADAY FORTE, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving MOPADAY FORTE, the patient should be observed closely for hypoglycaemia.

Topiramate
A decrease in the exposure of pioglitazone and its active metabolites were noted with concomitant administration of pioglitazone and topiramate. The clinical relevance of this decrease is unknown; however, when MOPADAY FORTE and topiramate are used concomitantly, monitor patients for adequate glycemic control.

4.6 Use in special populations
Pregnant women
Limited data with MOPADAY FORTE or pioglitazone in pregnant women are not sufficient to determine a 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.

In animal reproduction studies, no adverse developmental effects were observed when pioglitazone was administered to pregnant rats and rabbits during organogenesis at exposures up to 5- and 35-times the 45 mg clinical dose, respectively, based on body surface area. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 2- to 6¬ times, respectively, a 2000 mg clinical dose, based on body surface area. 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

Lactation
There is no information regarding the presence of MOPADAY FORTE or pioglitazone in human milk, the effects on the breastfed infant, or the effects on milk production. Pioglitazone is present in rat milk; however, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels 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. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MOPADAY FORTE and any potential adverse effects on the breastfed infant from MOPADAY FORTE or from the underlying maternal condition.

Pediatric Use
Safety and effectiveness of MOPADAY FORTE in pediatric patients have not been established. MOPADAY FORTE is not recommended for use in pediatric patients based on adverse effects observed in adults, including fluid retention and congestive heart failure, fractures, and urinary bladder tumors.

Geriatric Use
Pioglitazone
In pharmacokinetic studies with pioglitazone, no significant differences were observed in pharmacokinetic parameters between elderly and younger patients

Metformin hydrochloride
Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. 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
Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. MOPADAY FORTE is contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m2.

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

4.7 Effects on ability to drive and use machines
No specific recommendations

4.8 Undesirable effects
Upper respiratory tract infection, edema, diarrhea, headache and weight gain, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, headache, sinusitis, myalgia, pharyngitis, edema, hypoglycemia, cardiac failure, pain in extremity, back pain, chest pain, elevated hepatic enzymes (serum ALT), hypoglycemia, urinary bladder tumor.

Any suspected adverse event can be reported to Wockhardt Pharmacovigilance at PVSafety@wockhardt.com or by calling at toll-free number 1800-258-8127 (All working days 9:00 AM to 5:00 PM). You can also report directly to Pharmacovigilance Progrm of India (PvPI) via helpline 1800-180-3024 (All working days 9:00 AM to 5:30 PM) or through "ADR PvPI" app.

Congestive heart failure
Thiazolidinediones, including pioglitazone, which is a component of MOPADAY FORTE, cause or exacerbate congestive heart failure in some patients. After initiation of MOPADAY FORTE, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of MOPADAY FORTE must be considered. MOPADAY FORTE is not recommended in patients with symptomatic heart failure. Initiation of MOPADAY FORTE in patients with established NewYork Heart Association (NYHA) Class III or IV heart failure is contraindicated.

Lactic acidosis
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 greater than 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 MOPADAY FORTE and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

Fractures
Increased incidence in female patients. Apply current standards of care for assessing and maintaining bone health

Cardiovascular Safety
There was no statistically significant difference between pioglitazone and placebo for the three-year incidence of a first event within this composite, there was no increase in mortality or in total macrovascular events with pioglitazone.

PROactive: Number of First and Total Events for Each Component within the Cardiovascular Composite Endpoint

	Placebo N=2633		Pioglitazone N=2605	
Cardiovascular Events	First Events n (%)	Total Events n	First Events n (%)	Total Events n
Any event	572 (21.7)	900	514 (19.7)	803
All-cause mortality	122 (4.6)	186	110 (4.2)	177
Non-fatal myocardial infarction (MI)	118 (4.5)	157	105 (4.0)	131
Stroke	96 (3.6)	119	76 (2.9)	92
Acute coronary syndrome	63 (2.4)	78	42 (1.6)	65
Cardiac intervention (CABG/PCI)	101 (3.8)	240	101 (3.9)	195
Major leg amputation	15 (0.6)	28	9 (0.3)	28
Leg revascularization	57 (2.2)	92	71 (2.7)	115

CABG = coronary artery bypass grafting; PCI = percutaneous intervention

Laboratory Abnormalities: Decrease in hemoglobin and haematocrit, lower serum vitamin B12 concentrations, elevation in CPK.

Weight Gain
Dose-related weight gain occurs when pioglitazone is used alone or in combination with other antidiabetic medications. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Edema
Edema induced from taking pioglitazone is reversible when pioglitazone is discontinued. The edema usually does not require hospitalization unless there is coexisting congestive heart failure.
In the 24-week trial, edema was reported in 3.0% of patients in the pioglitazone+metformin group, 4.2% in the pioglitazone monotherapy group, and 1.4% in the metformin monotherapy group.

4.9 Overdose
Pioglitazone
During controlled clinical trials, one case of overdose with pioglitazone was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.
Metformin hydrochloride
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 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 metformin from patients in whom metformin overdosage is suspected.

5. Pharmacological properties
MOPADAY FORTE combines two antidiabetic medications with different mechanisms of action to improve glycemic control in adults with type 2 diabetes: pioglitazone, a thiazolidinedione, and metformin hydrochloride, a biguanide.

5.1 Mechanism of Action
Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas biguanides act primarily by decreasing endogenous hepatic glucose production.
Pioglitazone
Pioglitazone is a thiazolidinedione that depends on the presence of insulin for its mechanism of action. Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Pioglitazone is not an insulin secretagogue. Pioglitazone is an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism. In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin dependent tissues and are observed in numerous animal models of insulin resistance. Because pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Metformin hydrochloride
Metformin hydrochloride 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 healthy subjects 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
Pioglitazone improves insulin sensitivity in insulin-resistant patients. Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal and improves hepatic sensitivity to insulin. In patients with type 2 diabetes, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations, and lower HbA1c values. Pioglitazone has an additive effect on glycemic control when used in combination with a sulfonylurea, metformin, or insulin.

Metformin hydrochloride 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.

5.3 Pharmacokinetic properties
Absorption
Pioglitazone
Following once-daily administration of pioglitazone, steady-state serum concentrations of both pioglitazone and its major active metabolites, M-III (keto derivative of pioglitazone) and M-IV (hydroxyl derivative of pioglitazone), are achieved within seven days. At steady-state, M-III and M-IV reach serum concentrations equal to or greater than that of pioglitazone. At steady-state, in both healthy volunteers and patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations (pioglitazone plus active metabolites) and 20% to 25% of the total AUC. Cmax, AUC, and trough serum concentrations (Cmin) for pioglitazone and M-III and M-IV, increased proportionally with administered doses of 15 mg and 30 mg per day.
Following oral administration of pioglitazone, Tmax of pioglitazone was within two hours. Food delays the Tmax to three to four hours, but does not alter the extent of absorption (AUC).

Metformin hydrochloride
Following a single oral dose of metformin 1000 mg ER, Cmax is achieved with a median value of
7 hours and a range of 4 to 8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of metformin IR, however, the extent of absorption (as measured by AUC) is similar. Peak plasma levels are approximately 1.1 µg/mL for 1000 mg once-daily doses.

Distribution
Pioglitazone
The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. M-III and M-IV are also extensively bound (>98%) to serum albumin.
Metformin hydrochloride
The Vd/F of metformin averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

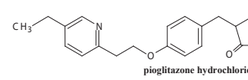
Metabolism
Pioglitazone
Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are the major circulating active metabolites in humans.
Metformin hydrochloride
Intravenous single-dose 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) nor biliary excretion.

Excretion and Elimination
Pioglitazone
Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.
The mean serum half-life (t1/2) of pioglitazone and its metabolites (M-III and M-IV) range from three to seven hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be five to seven L/hr.
Metformin hydrochloride
Renal clearance is approximately 3.5 times greater than creatinine clearance (CLcr), 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 t1/2 of approximately 6.2 hours. In blood, the elimination t1/2 is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

6. Nonclinical properties
Carcinogenesis, Mutagenesis, Impairment of Fertility
Pioglitazone
Pioglitazone hydrochloride was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and A552/XPRT), an in vitro cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an in vivo micronucleus assay. No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone hydrochloride daily prior to and throughout mating and gestation (approximately nine times the maximum recommended human oral dose based on mg/m2).
Metformin
There was no evidence of 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.

Animal Toxicology and/or Pharmacology
Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone hydrochloride (approximately 11, one, and two times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of
8.9 mg/kg and above (approximately four times the maximum recommended human oral dose based on mg/m2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m2).

7. Description
MOPADAY FORTE tablets are a thiazolidinediones and biguanide combination product that contains two oral antidiabetic medications: pioglitazone hydrochloride and metformin hydrochloride.
Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone interconvert in vivo. No differences were found in the pharmacologic activity between the two enantiomers. The structural formula is as shown:



pioglitazone hydrochloride

Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S$·HCl and a molecular weight of 392.90 daltons. It is soluble in N,N-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a white crystalline powder with a molecular formula of $C_4H_{11}N_5$·HCl and a molecular weight of 165.62. 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 as shown:

metformin hydrochloride

8. Pharmaceutical particulars

8.1 Incompatibilities
There are no known incompatibilities

8.2 Shelf-life
24 months.

8.3 Packaging information
Blister pack of 1X10 tablets

8.4 Storage and handing instructions
Store in a dry place at temperature not exceeding 30° C, protected from moisture.

9. Patient Counselling Information
- It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated hemoglobin tested regularly. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.
- Tell patients to promptly report any sign of macroscopic hematuria or other symptoms such as dysuria or urinary urgency that develop or increase during treatment as these may be due to bladder cancer.
- Explain to patients the risks of lactic acidosis, its symptoms and conditions that predispose to its development, as noted in the Warnings and Precautions section. Advise patients to discontinue MOPADAY FORTE immediately and to promptly notify their healthcare professional if unexplained hyperventilation, myalgia, gastrointestinal symptoms, malaise, unusual somnolence, or other nonspecific symptoms occur. Instruct patients to inform their doctor that they are taking MOPADAY FORTE prior to any surgical or radiological procedure, as temporary discontinuation of MOPADAY FORTE may be required until renal function has been confirmed to be normal.
- Counsel patients against excessive alcohol intake while receiving MOPADAY FORTE.
- Inform patients to immediately report symptoms of an unusually rapid increase in weight or edema, shortness of breath, or other symptoms of heart failure while receiving MOPADAY FORTE.
- Tell patients to promptly stop taking MOPADAY FORTE and seek immediate medical advice if there is unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine as these symptoms may be due to hepatotoxicity.
- Inform patients about the importance of regular testing of renal function and hematologic parameters when receiving treatment with MOPADAY FORTE.
- Inform female patients that treatment with MOPADAY FORTE may result in an unintended pregnancy in some premenopausal anovulatory females due to its effect on ovulation
- Combination antihyperglycemic therapy may cause hypoglycemia. When initiating MOPADAY FORTE, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.
- Patients should be told to take MOPADAY FORTE as prescribed and instructed that any change in dosing should only be done if directed by their physician. If a dose is missed on one day, the dose should not be doubled the following day.

10. Details of manufacturer
Manufactured in India by
Tristar Formulations Pvt Ltd,
Plot No A -116 and A-117, 27th Cross, PIPDIC Industrial Estate
Mettupalayam, Puducherry- 605009

Marketed by
WOCKHARDT LTD.
Wockhardt Towers, Bandra Kurla Complex, Mumbai 400051

11. Details of permission or licence number with date
M.L.No. 04131106 valid up to 26.02.2024

12. Date of revision
Dec 21

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Front

Back

Unfolded size : 280 x 170 mm (LxW)

Pantone 199 C

K 100