Diaben®

Rosiglitazone Maleate 4 mg
Rosiglitazone Maleate 8 mg

Coated tablets

Made in Argentine
Sold under prescription.

Composition:
Each coated tablet of Diaben®4 mg contains: rosiglitazone maleate 5,30 mg (equivalent to 4 mg of rosiglitazone) Excipients: Nucleus: microcrystalline cellulose 29,95 mg; sodium starch glycolate 7,50 mg; lactose 104,5 mg; hydroxypropylmethylcellulose 2,00 mg; magnesium stearate 0,75 mg. Coat: polyethylene glycol 0,38 mg; hydroxypropylmethylcellulose 3,00 mg; red ferric oxide 0,02 mg; yellow ferric oxide 0,03 mg; titanium dioxide 0,15 mg.
Each coated tablet of Diaben®8 mg contains: rosiglitazone maleate 10,60 mg (equivalent to 8 mg of rosiglitazone) Excipients: Nucleus: microcrystalline cellulose 59,40 mg; sodium starch glycolate 15,0 mg; lactose 209,5 mg; hydroxypropylmethylcellulose 4,00 mg; magnesium stearate 1,50 mg. Coat: polyethyleneglycol 0,76 mg; hydroxypropylmethylcellulose 6,00 mg; red ferric oxide 0,12 mg; titanium dioxide 0,30 mg.

Therapeutical action:
Oral anti-diabetic. Code ATC A10BG.

Indications:
Diaben® is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Diaben® is indicated as monotherapy. Diaben® is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet, exercise, and a single agent do not result in adequate glycemic control. For patients inadequately controlled with a maximum dose of a sulfonylurea or metformin, Diaben® should be added to, rather than substituted for, a sulfonylurea or metformin.
Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but also in maintaining the efficacy of drug therapy. Prior to initiation of therapy with Diaben®, secondary causes of poor glycemic control, e.g., infection, should be investigated and treated.

Pharmacological characteristics:
Pharmacological action .
Mechanism of Action.
Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPAR gamma). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR gamma nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPAR gamma-responsive genes also participate in the regulation of fatty acid metabolism. Insulin resistance is a common feature characterizing the pathogenesis of type 2 diabetes. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia. Rosiglitazone does not induce hypoglycemia.

Pharmacokinetics.
Maximum plasma concentration (C max) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range. The elimination half-life is 3 to 4 hours and is independent of dose.

Absorption.
Absolut bioavailability of rosiglitazone is of the 99 Peak plasma concentrations are observed about 1 hour after dosing. Administration of rosiglitazone with food resulted in no change in overall exposure (AUC) but there was an approximately 28% decrease in C max and a delay in T max (1.75 hours). These changes are not likely to be clinically significant; therefore Diaben®, may be administered with or without food.
Distribution.
The mean (CV%) oral volume of distribution (Vss/F) of rosiglitazone is approximately 17.6 (30%) liters. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

Metabolism.
Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone. Rosiglitazone is predominantly metabolized by Cytochrome P 450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway.

Excretion.
Following oral or intravenous administration of [14 C] rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [14 C] related material ranged from 103 to 158 hours.
Pharmacokinetics in patients with type 2 Diabetes.
The pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption.

Special populations.
-Age: Age does not significantly affect the pharmacokinetics of rosiglitazone.
-Gender: the mean oral clearance of rosiglitazone in female patients was approximately 6% lower compared to male patients of the same body weight. As monotherapy and in combination with metformin, rosiglitazone improved glycemic control in both males and females. In metformin combination, efficacy was demonstrated with no gender differences in glycemic response. In monotherapy , a greater therapeutic response was observed in females; however,in more obese patients, gender differences were less evident. For a given body mass index(BMI), females tend to have a greater fat mass than males. Since the molecular target PPAR gamma is expressed in adipose tissues this differentiating characteristic may account, at least in part, for the greater response to rosiglitazone in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.
-Hepatic Impairment: unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child- Pugh Class B/C) compared to healthy subjects. As a result,unbound C max and AUC 0-inf were increased 2-and 3-fold,respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects. Therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT> 2,5 Over the normal limit) (see **Precautions**, Hepatic effects).
-Renal Impairment: there are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function. No dosage adjustment is therefore required in such patients receiving rosiglitazone. Since metformin is contraindicated in patients with renal impairment, co-administration of metformin with rosiglitazone is contraindicated in these patients.
-Race: race has no influence on the pharmacokinetics of rosiglitazone.
-Pediatric Use: the safety and effectiveness of rosiglitazone in pediatric patients have not been established.

Pharmacodynamics and Clinical effects:
Treatment with rosiglitazone resulted in an improvement in glycemic control, as measured by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c), with a concurrent reduction in insulin and C-peptide. Postprandial glucose and insulin were also reduced. This is consistent with the mechanism of action of rosiglitazone as an insulin sensitizer. The improvement in glycemic control was durable, with maintenance of effect . The maximum recommended daily dose is 8 mg. No additional benefit was obtained with a total daily dose of 12 mg.

Dosage and Administration form:
The management of antidiabetic therapy should be individualized.
Monotherapy.
The usual starting dose of Diaben® is 4 mg administered either as a single dose once daily or in divided doses twice daily. For patient that did not respond right after 12 weeks of treatment according to plasma glucose reduction in fast, the dose can be increased to 8 mg administered as single dose daily.
Therapy combined with metformin.
The usual starting dose of Diaben® in combination with metformin is 4 mg administered as either a single dose once daily or in divided doses twice daily Rosiglitazone can be increased to 8 mg /day in the following 12 weeks since initiation of treatment,if reduction in fasting plasma glucose was insufficient. Diaben® can be administered as a single dose in the morning or it can be divided and administered in the morning and at night.
Therapy combined with Sulfonylureas:
When used in combination with sulfonylurea, the recommended dose of Diaben® is 4 mg administered as either a single dose once daily or in divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased. Doses of Diaben® greater than 4 mg daily in combination with a sulfonylurea have not been studied in adequate and well-controlled clinical trials. Due to the low incidence of hypoglycemia when 4 mg of rosiglitazone combined with sulfonylureas are used daily, the patients who are suitably controlled with 4 mg/day of rosiglitazone can benefit by means of cautious adjustment of dose to 8 mg/ day. Diaben® dose can be increased in the 8-12 weeks following initiation of the therapy if there is an insufficient reduction in the fasting plasma glucose. In order to optimize the therapy, a reduction in the sulfonylureas dose may be required.
Periodic plasma glucose measurements in fasting state would be made with the purpose of watching the therapeutical responsé, prior to the establishment of the dose. Diaben® may be taken with or without food. No dosage adjustments are required for the elderly. No dosage adjustment is necessary when Diaben® is used as monotherapy in patients with renal impairment. Since metformin is contraindicated in such patients, concomitant administration of metformin and Diaben® is also contraindicated in patients with renal impairment. Therapy with Diaben® should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5 _ upper limit of normal at start of therapy).
There are no data on the use of Diaben® in patients younger than 18 years; therefore, use of Diaben® in pediatric patients is not recommended.

Contraindications:
Rosiglitazone is contraindicated in patients with known hypersensitivity to this product or any of its components.

Warnings and precautions:
Due to its mechanism of action, Diaben® is active only in the presence of endogenous insulin. Therefore, Diaben® should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
-Ovulation: rosiglitazone like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking Diaben®. Thus, adequate contraception in premenopausal women should be recommended. Although hormonal imbalance has been seen (see **Precautions**,Carcinogenesis, Mutagenesis, Impairment of Fertility), the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with Diaben® should be reviewed.

- Edema: Diaben® should be used with caution in patients with edema. Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, Diaben® should be used with caution in patients at risk for heart failure (particularly those with insulin) and should be monitored for signs and symptoms of heart failure. (See **Precautions**, Use in cardiac insufficiency patients)
-Use in patients with cardiac failure: thiazolidinediones, including rosiglitazone increase plasma volume and cardiac failure by proload. Diaben did not demonstrate harmful alteration in cardiac structure or function. Rosiglitazone is not indicated in patients with cardiac failure in stages 3 and 4 of NYHA, unless the expected benefit exceeds the potential risk. Adverse effects potentially related to the volume expansion have been reported.
-Patients with hepatic antecedents: in hepatic antecedents patients it is recommended that the clinic and the hepatic enzymes value be controlled. The decision of continuing the treatment must be taken by means of the clinical observation, in the view of the laboratory results.
If jaundice is observed, the treatment will have to be interrupted.

Interactions:
Drugs Metabolized by Cytochrome P 450.
Rosiglitazone does not inhibit any of the major P 450 enzymes at clinically relevant concentrations. Rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. Rosiglitazone (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinyl estradiol and norethindrone), which are predominantly metabolized by CYP3A4
-Metformin: concurrent administration of rosiglitazone and metformin had no effect on the steady-state pharmacokinetics of either metformin or rosiglitazone.
-Acarbose: coadministration of acarbose had no relevant effect on the pharmacokinetics over rosiglitazone.
-Digoxin: repeat oral dosing of rosiglitazone did not alter the steady-state pharmacokinetics of digoxin.
-Warfarin: repeat dosing with rosiglitazone had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers
-Ethanol: a single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in type 2 diabetes mellitus patients treated with rosiglitazone.
-Ranitidine: pretreatment with ranitidine did not alter the pharmacokinetics of either single oral or intravenous doses of rosiglitazone. These results suggest that the absorption of oral rosiglitazone is not altered in conditions accompanied by increases in gastrointestinal pH.
-Impairment of Fertility: rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day.
Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower levels of progesterone and estradiol. No such effects were noted at 0.2 mg/kg/day.
Rosiglitazone diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

Pregnancy and nursing:
Pregnancy.
-There are no adequate and well-controlled studies in pregnant women. Rosiglitazone should not be used during pregnacy unless potential benefits exceeds potential risk for the fetus. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.
Labor and Delivery.
-The effect of rosiglitazone on labor and delivery in humans is not known.
-Lactating women period: drug-related material was detected in milk from lactating rats.
It is not known whether rosiglitazone is excreted in human milk.
Because many drugs are excreted in human milk, rosiglitazone should not be administered to a nursing woman.
Effect over driving and machine use capacity.
-Rosiglitazone does not produce sleepiness and it is not associated with hypoglycemia.
Should not diminish the ability to drive neither the ability to handle machines.

Adverse Effects:
The incidence and types of adverse events of rosiglitazone as monotherapy are:
-Upper respiratory tract infection.
-Headache.
-Back pain.
-Hyperglycemia.
-Fatigue.
-Sinusitis.
-Diarrhea.
-Hypoglycemia.
Anemia and Edema were also reported as adverse effect, which were mild to moderate in severity and did not require discontinuation of treatment.
Laboratory abnormalities.
-Hematologic: decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in patients treated with rosiglitazone.
White blood cell counts also decreased slightly in patients treated with rosiglitazone.
Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with rosiglitazone.
-Lipids: changes in serum lipids have been observed following treatment with rosiglitazone.
Serum Transaminase Levels.
Patients treated with rosiglitazone showed no evidence of drug-induced hepatotoxicity or elevated ALT levels.
No reports of hepatic enzyme elevations or alterations.

KEEP THIS AND ALL MEDICINES OUT OF CHILDREN

REACH. Overdosage:
Limited data are available with regard to overdosage in humans.
In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

Patient information.
It should be informed to patients that treatment of type 2 diabetes mellitus should include diet control. Restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity.
This is important not only in the primary treatment of type 2 diabetes, but also in maintaining the efficacy of drug therapy.
Rosiglitazone can be taken with or without food.
The use of rosiglitazone can result in ovulation in premenopausal anovulatory women with insulin resistance. Therefore contraceptive should be suggested.

Storage:
Keep between 15 and 30 ° C, in well close package.

Presentations:
Diaben® 4 mg y Diaben® 8 mg: is presented in packages containing 15 coated tablets.

Speciality authorized by Ministry of Health and Enviroment.
Certificate N° 50.974
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