PRODUCT MONOGRAPH

METFORMIN-500
METFORMIN-850

Metformin Hydrochloride Tablets

500 mg and 850 mg

Oral Antihyperglycemic Agent

PRO DOC LIMITÉE
Laval QC H7L 3W9

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THERAPEUTIC CLASSIFICATION

Oral Antihyperglycemic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Metformin HCl is a biguanide derivative producing an antihyperglycemic effect which can only be observed in man or in a diabetic animal and only when there is insulin secretion. Metformin at therapeutic doses, does not cause hypoglycemia when used alone in man or in the non–diabetic animal, expept when using a near lethal dose. Metformin has no effect on the pancreatic beta cells. The mode of action of metformin is not fully understood. It has been postulated that metformin might potentiate the effect of insulin or that it might enhance the effect of insulin on peripheral receptor sites. This increased sensitivity seems to follow an increase in the number of insulin receptors on cell surface membranes.

Metformin absorption is relatively slow and may extend over about 6 hours. The drug is excreted in urine at a high renal clearance rate of about 450 mL/min. The initial elimination of metformin is rapid, with a half–life varying between 1.7 and 3 hours. The terminal elimination phase accounting for about 4 to 5% of the absorbed dose is slow with a half–life between 9 and 17 hours. Metformin is not metabolized. Its main sites of concentration are the intestinal mucosa and the salivary glands. The plasma concentration at steady state ranges about 1 to 2 µg/mL. Certain drugs may potentiate the effects of metformin (see PRECAUTIONS).

A two–way, balanced, randomized cross–over bioavailability study was conducted in 19 healthy, adult male volunteers to evaluate the relative bioavailability of single oral doses (500 mg) of **METFORMIN-500 mg** tablets and Glucophage® 500 mg tablets. One subject withdrew after the first phase (reason unknown), therefore, only eighteen subjects completed the study. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data
Metformin Tablets (1x500 mg)

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Means (%)
	METFORMIN-500	Glucophage®*	
AUC_T (ng•hr/mL)	7180 7447 (29)	6912 7213 (30)	104
AUC_I (ng•hr/mL)	7347 7606 (29)	7080 7374 (30)	104
C_{max} (ng/mL)	1167 1196 (23)	1107 1127 (19)	105
T_{max} (hr)	2.50 (0.81)	2.50 (1.07)	–
$t_{½}$ (hr)	3.05 (0.70)	3.18 (0.66)	–

The T_{max} and $t_{½}$ parameters are expressed as the arithmetic means (standard deviations).
*Glucophage® (Marion Merrell Dow Canada) was purchased at a Canadian retail pharmacy.

INDICATIONS AND CLINICAL USE

To control hyperglycemia in METFORMIN (metformin HCl) responsive, stable, mild, non–ketosis prone, maturity onset type of diabetes (Type II) which cannot be controlled by proper dietary management, exercise and weight reduction or when insulin therapy is not appropriate. METFORMIN can be of value for the treatment of obese diabetic patients.

CONTRAINDICATIONS

METFORMIN (metformin HCl) is contraindicated in patients with unstable and/or insulin dependent (Type I) diabetes mellitus, history of ketoacidosis with or without coma.

In the presence of severe liver disease. In the presence of renal impairment or when renal function is not known, and also in patients with serum creatinine levels above the upper limit of the normal range.

In chronic alcoholism with hepatic damage.

In patients undergoing medical or diagnostic examinations, such as intravenous pyelography or angiography which could lead to a temporary functional oliguria (see WARNINGS).

In cases of cardiovascular collapse and in disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia.

In patients suffering from severe dehydration.

During stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter.

Known sensitivity or allergy to the drug.

In patients with a history of lactic acidosis irrespective of the precipitating factors.

During pregnancy.

WARNINGS

The use of METFORMIN. (metformin HCl) will not prevent the development of complications peculiar to diabetes mellitus.

Use of METFORMIN must be considered as treatment in addition to proper dietary regimen and not as a substitute for diet.

Care should be taken to ensure that METFORMIN is not given when a contraindication exists. If acidosis of any kind develops, METFORMIN should be discontinued immediately.

The risk of lactic acidosis increases with the degree of renal dysfunction, impairment of creatinine clearance and age of the patient. Patients with serum creatinine above the upper limit of the normal range should not receive METFORMIN.

If during METFORMIN therapy the patient develops acute intercurrent disease such as: clinically significant hepatic dysfunction, cardiovascular collapse, congestive heart failure, acute myocardial infarction, or other conditions complicated by hypoxemia, the drug should be discontinued.

In patients undergoing intravenous pyelography or angiography, METFORMIN should be discontinued 2 days prior to the procedure and therapy may be reinstituted after the renal function has been re–evaluated.

Discontinue METFORMIN 2 days before a surgical intervention. Therapy may be reinstituted following the operation after the renal function has been re–evaluated.

Patients should be warned against using alcohol in excess while on METFORMIN therapy. Alcohol in a diabetic subject may cause an elevation of blood lactate.

PRECAUTIONS

Patient Selection and Follow–Up:

Careful selection of patients is important. It is imperative that there be rigid attention to diet and careful adjustment of dosage. When METFORMIN (metformin HCl) is combined with a sulfonylurea, instruct the patient on hypoglycemic reactions and their control. Regular thorough follow–up examinations are necessary (see WARNINGS).

If vomiting occurs, withdraw drug temporarily, exclude lactic acidosis, then resume dosage cautiously (see ADVERSE REACTIONS).

Particular attention should be paid to short– and long–range complications which are peculiar to diabetes. Periodic cardiovascular, ophthalmic, hematological, hepatic and renal assessments are advisable (see WARNINGS).

Ascertain that the renal function is within normal range every 6 months while on METFORMIN therapy.

Impairment of vitamin B_{12} and folic acid absorption has been reported in some patients. Therefore, measurements of serum vitamin B_{12} and folic acid are advisable at least every one to two years in patients on long–term treatment with METFORMIN .

Drug Interactions

Certain drugs may potentiate the effect of METFORMIN , particularly sulfonylurea type of drugs used in the treatment of diabetes. The simultaneous administration of these two types of drugs could produce a hypoglycemic reaction, especially if they are given in patients already receiving other drugs which, themselves, can potentiate the effect of sulfonylureas such as long–acting sulfonamides, tuberculostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid and propranolol.

Other drugs tend to produce hyperglycemia and may lead to a loss of blood sugar control. These include diuretics (thiazides, furosemide), corticosteroids, oral contraceptives (estrogen plus progestogen) and nicotinic acid in pharmacologic doses.

Elimination rate of the anticoagulant, phenprocoumon, has been reported to be increased by 20% when used concurrently with metformin. Therefore, patients receiving phenprocoumon or other antivitamin K anticoagulants should be watched carefully when both types of drugs are used simultaneously. In such cases, an important increase of prothrombin time may occur upon cessation of metformin therapy, with an increased risk of hemorrhage.

Note: When used as indicated, there has not been a single case of lactic acidosis in Canada. Since its introduction in 1959, an estimated 600,000 patients are taking the drug world–wide. Twenty–eight cases of lactic acidosis have so far been reported and in each case a contraindication existed. METFORMIN should be immediately discontinued in the presence of acidosis.

Lactic acidosis is a serious and often fatal metabolic complication observed, among other conditions, in diabetic patients. It is characterized by acidosis (decreased blood pH); electrolyte disturbances with an increased anion gap and an increased lactate level with altered lactate–pyruvate ratio; azotemia may also be present. Physicians should instruct their patients to recognize the symptoms which could signal the onset of lactic acidosis.

ADVERSE REACTIONS

The most frequently reported adverse reactions with metformin are: metallic taste in the mouth, epigastric discomfort, nausea and vomiting; rarely, diarrhea and anorexia. Most of these reactions are transient and can be controlled by reducing the dosage or by discontinuing therapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Available information concerning treatment of a massive overdosage of metformin is very limited. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded. The drug should be discontinued and proper supportive therapy instituted.

DOSAGE AND ADMINISTRATION

In diabetic patients, individual determination of the minimum dose that will lower blood glucose adequately should be made.

In patients where on initial trial the maximal recommended dose fails to lower the blood glucose adequately, the drug should be discontinued. Deterioration of the patient's condition can occur during the treatment of diabetes. It is advisable to ascertain the contribution of the drug in the control of blood glucose by discontinuing the medication semi–annually or at least annually with careful monitoring of the patient. If the need for the drug is not evident, the drug should not be resumed. In some diabetic subjects, short–term administration of the drug may be sufficient during periods of transient loss of blood sugar control.

The usual dose is 500 mg three to four times a day, or 850 mg two or three times a day. Maximal dose should not exceed 2.5 g a day. To minimize gastric intolerance such as nausea and vomiting, METFORMIN (metformin HCl) should be taken with food whenever possible.

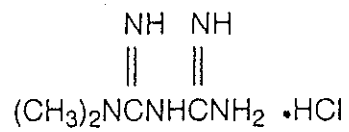
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Metformin hydrochloride

Chemical Name:
1) Imidodicarbonimidic diamide, *N,N*–dimethyl–, hydrochloride
2) 1,1–Dimethylbiguanide, hydrochloride

Structural Formula:



Molecular Formula: $C_4H_{11}N_5 \cdot HCl$

Molecular Weight: 165.6

Description: A white, crystalline powder; odourless or almost odourless; hygroscopic. Soluble 1 in 2 of water; slightly soluble in ethanol (96%); practically insoluble in chloroform and ether. Melting point, approximately 225°C.

Composition

METFORMIN (metformin HCl) 500 mg and 850 mg tablets contain the following non–medicinal ingredients: methylcellulose and magnesium stearate.

Stability and Storage Recommendations

METFORMIN (metformin HCl) tablets should be stored at controlled room temperature (15–30°C) in tightly–closed containers.

AVAILABILITY OF DOSAGE FORMS

Each white, round, flat–faced, bevelled–edge tablet, scored and engraved "PRO" over "M500" on one side, contains: metformin HCl 500 mg. Bottles of 100, 250, 500 and 1,000.

Each white, capsule–shaped tablet, engraved "PRO" on one side and "850" on the other, contains: metformin HCl 850 mg. Bottles of 100, 250 and 500.

PHARMACOLOGY

Metformin absorption is relatively slow and may extend over about 6 hours.

Animal studies with metformin, labelled with ^{14}C have shown that the drug is neither concentrated by liver cells nor is it excreted in the bile; it is concentrated in the intestinal mucosa and salivary glands.

It has been shown that, following a 2 g dose of metformin, the blood level remains under 10 mcg/mL even at the peak, occurring 2 hours after absorption. During the experiments, metformin was shown to be devoid of any notable action in the body, apart from its specific metabolic activity.

In the healthy animal, metformin lowers blood sugar only at a nearly lethal dose. Different animal species are of unequal sensitivity. On the other hand, the animal with experimental diabetes is sensitive to a much lower dosage, providing some insulin is still secreted.

The antihyperglycemic action of metformin is probably mediated through insulin.

Metformin improves the K coefficient of glucose assimilation and the coefficient of insulin efficiency.

In the obese diabetic with hyperinsulinemia, metformin is reported to normalize insulin output. This normalizing effect is concurrent to that of glycemia.

Metformin has little effect on liver glycogen of the healthy animal. In low and average doses, no change occurs. In high doses nearing lethal levels, liver glycogen decreases. This lowering precedes the fall in blood sugar. This reaction represents a defence mechanism tending to mobilize body reserves in order to combat hypoglycemia.

In the diabetic animal with a low liver glycogen reserve, the opposite occurs and metformin builds up glycogen stores of the liver. *In vitro*, on muscular tissue isolated in Warburg's apparatus, metformin increases glucose uptake by the muscle. This action follows an aerobic pathway. Even in high concentration, contrary to phenethylbiguanide, metformin apparently does not block respiration or change carbohydrate metabolism via the anaerobic pathway.

Metformin is eliminated in feces and urine. It is rapidly excreted by the kidneys in an unchanged form.

Renal clearance is 450 mL/minute; this appears to explain the absence of accumulation.

Metabolites of metformin have not been identified, neither by radioactive nor by chemical methods.

A single Rf spot is always present following radiochromatographic study of urine and always corresponds to that of pure metformin. Administration during 10 consecutive days has not shown any sign of accumulation.

Inhibition of glyconeogenesis has been observed in animals following its stimulation by fasting, cortisol, alcohol or other substrates such as alanine, lactate or pyruvate. However, such an effect varies according to the type and dosage of the biguanide used, nutritional state of the animal, species and design of experimental model.

This inhibition of glyconeogenesis is observed only in the presence of insulin and it does not appear to play an important role in man.

Inhibition of intestinal absorption of sugars, which is not related to a malabsorption phenomenon has been observed with biguanides under certain experimental conditions in animals and in man. In one study, a 20% retardation of galactose absorption was observed in man receiving metformin. However, such an effect of metformin could not be confirmed in another study in man.

Recent findings appear to indicate that most of the metabolic effects of the biguanides are exerted through a single mechanism, namely inhibition of fatty acid oxidation and of acetyl–CoA generation.

However, inhibition of insulin–stimulated lipogenesis which has also been observed appears to be due to the inhibition of acetyl–CoA carboxylase by the biguanides. Such an effect may explain, at least partly, the weight–reducing effect exerted by these drugs in obese diabetic patients.

TOXICOLOGY

ANIMAL TOXICITY

Acute Toxicity (LD_{50})

Animal	Subcutaneously	Orally
Mouse	225 mg/kg	3,500 mg/kg
Chicken	150 mg/kg	
Rat	300 mg/kg	1,000 mg/kg
Rabbit	150 mg/kg	350 mg/kg
Guinea Pig	150 mg/kg	500 mg/kg

Chronic Toxicity

A) The following doses of metformin produced no organ toxicity:

Rats	125 mg/kg	per os for one year
Rabbits	100 mg/kg	per os for one year
Dogs	50 mg/kg	subcutaneously for 2 years

Acute or chronic organ toxicity was not produced in the animal species involved.

B) A study was carried out during 9 months with 80 rats, male and female, divided in 4 groups, with the following dosage regimen:

1st Group	Control
2nd Group	150 mg/kg per os
3rd Group	300 mg/kg per os
4th Group	300 mg/kg per os, dose increased by 100 mg/kg/day every 15 days

In summary, the authors report the excellent tolerance of metformin by rats, even when administered in very high doses. No drug–related lesion has been observed.

C) Chronic toxicity studies of 9 months duration were carried through with 16 beagle dogs, although the complete intolerance of this animal species to oral hypoglycemic agents is a well established fact. Trophic and neurologic disorders with cachexia rapidly lead to the dog's death. During the periods of metformin administration, laboratory findings were within normal limits. The levels of enzymes were somewhat elevated, but it is difficult to ascribe a pathological significance to their values, since subjects in the control group were at the same level as treated animals.

Pathological studies show an extreme degree of undernutrition in all metformin treated animals. Profound wasting especially marked in fat tissues was evident in all organs. Cachexia appears as the common cause of death of these animals.

HUMAN TOXICITY

In man, no adverse effect has been reported on liver or kidney function, the hematopoietic system or on the blood vessels. Twenty–eight cases of lactic acidosis among an estimated 600,000 patients receiving metformin therapy have been reported.