**NON-ANNOTATED**

# PRODUCT MONOGRAPH

# METFORMIN

(Metformin hydrochloride tablets BP)

**500 mg**

Antihyperglycemic Agent

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Date of Preparation:

September 30, 1998

Control Number: 058176

NAME OF DRUG

METFORMIN
(metformin hydrochloride tablets BP)
500 mg

## THERAPEUTIC CLASSIFICATION

Antihyperglycemic Agent

## ACTIONS AND CLINICAL PHARMACOLOGY

Metformin is a biguanide derivative producing an antihyperglycemic effect which can only be observed in man or in the 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 nondiabetic animal, except when using a near lethal dose. Metformin has no effects 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.

**Pharmacokinetics:** 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 comparative bioavailability study of metformin 850 mg tablets was performed. Pharmacokinetic and bioavailabilty data were measured in 26 volunteers in the *fasting* state. The results can be summarized as follows:

## SUMMARY OF COMPARATIVE BIOAVAILABILITY DATA

[single 850 mg tablet oral administration in the fasting state]

METFORMIN 850 mg Tablets

*versus*

Glucophage 850 mg Tablets (Hoechst Marion Roussel Canada Inc., Canada, Lot# 9559)

**Measured Data**

| Parameter | Geometric Mean<br>Arithmetic Mean (CV%)<br>Test | Reference | Ratio of Geometric Means (%)<br>(90% Confidence Limit) |
|---|---|---|---|
| $AUC_T$<br>(ng•h/mL) | 9133.8<br>9419.6 (26.2) | 9043.4<br>9444.7 (29.6) | 101<br>(95 - 107) |
| $AUC_\infty$<br>(ng•h/mL) | 9398.2<br>9688.9 (26.0) | 9307.7<br>9711.8 (29.5) | 101<br>(95 - 107) |
| $C_{max}$<br>(ng/mL) | 1581.3<br>1633.7 (26.4) | 1528.5<br>1586.9 (27.2) | 103 |
| $T_{max}$<br>(h) | 2.73 (36.6) | 2.58 (38.6) | ---- |
| $T½_{el}$<br>(h) | 2.84 (29.6) | 2.76 (22.5) | ---- |

***$T_{max}$ and $T½_{el}$*** **-- presented as the arithmetic means with CV in parenthesis.**

## INDICATIONS

To control hyperglycemia in metformin responsive stable, mild, nonketosis 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

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 i.v. pyelography or angiography which could lead to 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.

Pregnancy: During pregnancy.

## WARNINGS

Metformin 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 the 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 an 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 i.v. 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 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 the drug temporarily, exclude lactic acidosis and then resume dosage cautiously (see Adverse Effects).

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 the 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 1 to 2 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. These drugs can be: long-acting sulfonamides, tuberculostatics, phenylbutazone, clofibrate, MAO inhibitors salicylates, probenecid and propranolol.

Other drugs tend to produce hyperglycemia and may lead to 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 in 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 worldwide. 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 onset of lactic acidosis.

## ADVERSE EFFECTS

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

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

**Symptoms and Treatment:** 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 the blood glucose adequately should be made.

In patients where, on initial trial, the maximal recommended dose fails to lower the blood glucose adequately, metformin 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 3 to 4 times a day. Maximal dose should not exceed 2.5 g a day. To minimize gastric intolerance such as nausea and vomiting, metformin should be taken with food whenever possible.

## PHARMACEUTICAL INFORMATION

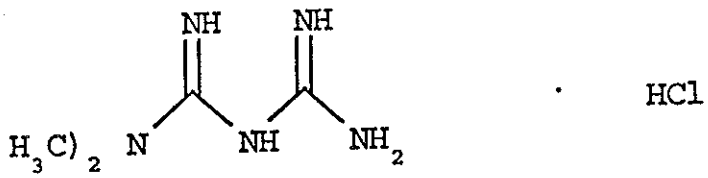
*DRUG SUBSTANCE*

Brand Name: METFORMIN

Proper Name: metformin hydrochloride

Chemical Name: N,N-dimethyldiguanide hydrochloride

Structural Formula:




Molecular Formula: $C_4H_{12}ClN_5$

Molecular Weight: 165.67

Description: Metformin occurs as a white crystalline powder, soluble in water and in ethyl alcohol 95%, practically insoluble in ether and in chloroform. It has a pKa of 2.8; 11.5 and a melting point of 224° - 229°C.

Composition:

pms-METFORMIN 500 mg Tablets contain: 500 mg metformin hydrochloride, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone PVK-90 and pregelatinized starch.

## AVAILABILITY OF DOSAGE FORMS

METFORMIN 500 mg Tablets are round, white, biconvex, coated and imprinted "METFORMIN 500" on one side and scored on the other. They are available in white HDPE bottles of 100 and 500 tablets.

tablets.

## STABILITY AND STORAGE RECOMMENDATIONS

Store at controlled room temperature (15°-30°C).

## PHARMACOLOGY

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

Animal studies with metformin, labelled with $C^{14}$ 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 mg/L 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 the 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 co-efficient of glucose assimilation. Metformin improves the co-efficient 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 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. 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 carboxylase by the biguanides. Such an effect may explain, at least partly, the weight-reducing effect by these drugs in obese diabetic patients. Metformin is eliminated in feces and urine. It is rapidly excreted by the kidneys in an unchanged form. Renal clearance is 130 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 animal and 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 carboxylase by the biguanides. Such an effect may explain, at least partly, the weight-reducing effect by these drugs in obese diabetic patients.

## TOXICOLOGY

1. Animal Toxicity

**Acute Toxicity $LD_{50}$**

| Animal | Subcutaneously | Orally |
|---|---|---|
| Mouse | 225 mg/kg | 3500 mg/kg |
| Chicken | 150 mg/kg | 1000 mg/kg |
| Rat | 300 mg/kg | 350 mg/kg |
| Rabbit | 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 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.

2. Human Toxicity

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

No case has ever been reported in Canada.

The consecutive administration of both phenformin and metformin to the same patient has allowed for the demonstration of a fundamental difference between these two biguanides in relation to lactacidemia. In some instances, patients developed hyperlactacidemia with phenformin when the same patients were presenting normal lactic acid levels while being treated with metformin. In other instances, hyperlactacidemia observed during a treatment with phenformin did regress when metformin was substituted for phenformin. Metformin may increase lactacidemia but to a degree that is clinically less significant than the elevation seen after phenformin.

## TERATOLOGY

Teratological studies were carried out in albino rats divided in three groups.

No abnormalities were found, even when high doses were administered. The number of animals was the same in each group.

Death rate in the three groups of treated animals and controls was approximately the same. However, the number of living animals in each group treated was slightly lower than in the control group. Also, the frequency of litters exceeding 10 live animals was slightly higher in the control group. A loss of weight at the time of weaning has been observed when compared to the control group.

Nevertheless, on a statistical basis, differences were shown to be non-significant. There is no difference between the groups of treated animals and the control group regarding the number of stillborn. The number of deaths after birth was slightly higher in metformin treated groups than in the control group, but the comparison of average death rates is not significant ($p>0.05$).

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