PRODUCT INFORMATION
METFORMIN SANDOZ® 500mg AND 850mg FILM COATED TABLETS

Life threatening lactic acidosis can occur due to accumulation of metformin. Risk factors include renal impairment. Other risk factors include old age associated with reduced renal function and high doses of metformin above 2 g/day.

NAME OF THE MEDICINE

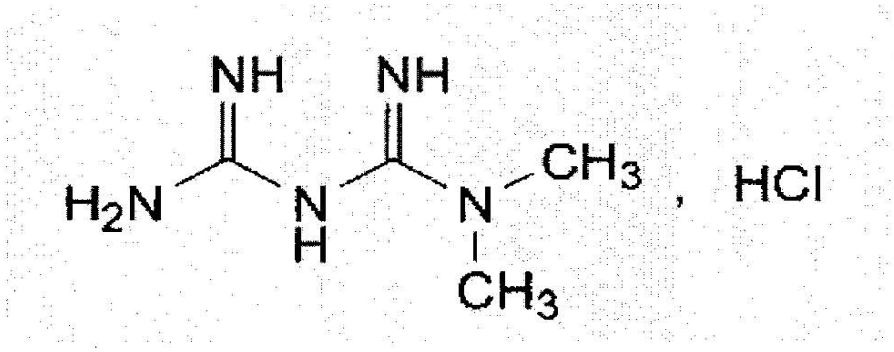
Generic name: Metformin hydrochloride.

Chemical name: 1,1-dimethylbiguanide hydrochloride.

Molecular formula: $C_4H_{11}N_5$,HCL.

MW: 165.6 CAS number: 1115-70-4

Chemical structure:



DESCRIPTION

Metformin hydrochloride is a white crystalline powder, which is odourless or almost odourless and hygroscopic. It is freely soluble in water, slightly soluble in alcohol and practically insoluble in acetone and in methylene chloride.

Composition
Active: Metformin Hydrochloride
Inactive: Sodium starch glycollate, maize starch, povidone, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide, propylene glycol, Macrogol 6000 and purified talc.

PHARMACOLOGY

Metformin is an antihyperglycaemic agent, which improves glucose tolerance in NIDDM subjects lowering both basal and post-prandial plasma glucose. Metformin causes an increased peripheral uptake of glucose by increasing the biological efficiency of available exogenous or endogenous insulin.

The mode of action of Metformin may be linked to increased insulin sensitivity. It does not stimulate insulin release but does require the presence of insulin to exert its antihyperglycaemic effect. Possible mechanisms of action include inhibition of gluconeogenesis in the liver, delay in glucose absorption from the gastrointestinal tract and an increase in peripheral uptake of glucose.

Metformin has an antiketogenic activity, which is comparable, though somewhat inferior to insulin itself.

Metformin has a modest favourable effect on serum lipids, which are often abnormal in NIDDM patients.

Pharmacokinetics:

Absorption: A randomised, open, balanced, crossover bioequivalence study using metformin tablets 500 mg film-coated tablets in 26 healthy subjects showed that peak plasma concentrations occurred at between 2 to 3 hours after a single dose of 500 mg. The mean peak plasma concentration was 0.721 mg/mL for the test product. Metformin was detected in plasma for 36 hours post dose in all subjects. The T_{max} values were comparable for both reference and test formulations. The 90% confidence limit for AUC_{0-t} and AUC_{0-inf} (as a measure of the extent of absorption) of the test product metformin tablets compared to the reference product (metformin 500 mg diabex Alphapharm) was within acceptable limits. No adverse events were reported.

After oral administration, metformin hydrochloride is absorbed along the entire gastrointestinal mucosa. Studies using single oral doses of metformin tablets indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than increase in elimination. At usual clinical doses and dosing schedules of metformin tablets, steady state plasma concentrations are reached in 24 to 48 hours and are generally less than 1 microgram/mL. Food decreases the extent and slightly delays the absorption of metformin. However the clinical relevance of this is unknown. During controlled trials, maximum metformin plasma levels did not generally exceed 5 micrograms /mL even at maximum doses.

Distribution: Metformin is negligibly bound to plasma proteins.

Metabolism: Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism.

Excretion: In patients with decreased renal function (based on measured creatinine clearance) the plasma half life of metformin is prolonged and renal clearance is decreased in proportion to the decrease in creatinine clearance, e.g. if creatinine clearance is 10-30 mL/min, renal

clearance is reduced to 20% of normal. No pharmacokinetic data is available for hepatic insufficiency.

CLINICAL TRIALS

The prospective randomized (UKPDS) study has established the long term benefit of intensive blood glucose control in type 2 diabetes.

Analysis of the results for overweight patients treated with metformin after failure of diet alone showed the following:

- a significant reduction of the absolute risk of any diabetes related complication in the metformin group (29.8 events/1000 patient years) versus diet alone (43.3 events/1000 patient years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1000 patient years), p=0.0034;

- a significant reduction of the absolute risk of diabetes related mortality; metformin 7.5 events/1000 patient years, diet alone 12.7 events/1000 patient years, p=0.017.

- A significant reduction of the absolute risk of overall mortality; metformin 13.5 events/1000 patient years versus diet alone 20.6 events/1000 patient years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1000 patient years (p=0.021).

- A significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient years, diet alone 18 events/1000 patient years (p=0.01)

For metformin used as second line therapy, in combination with a sulphonylurea, benefit regarding clinical outcome has not been shown.

In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

INDICATIONS

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone, does not result in adequate glycaemic control.

Metformin may be used as initial treatment, or in sulphonylurea failures, either alone or in combination with a sulphonylurea and other oral agents or as adjuvant therapy in insulin dependent diabetes.

CONTRAINDICATIONS

- Juvenile diabetes mellitus that is uncomplicated and well-regulated on insulin.

- Diabetes mellitus regulated by diet alone.
- During or immediately following surgery where insulin is essential.
- Hypersensitivity to metformin hydrochloride or to any of the excipients listed (see COMPOSITION).
- Diabetic ketoacidosis, diabetic pre-coma
- Renal failure or renal dysfunction (creatinine clearance < 60 mL/minute).
- Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock, intravascular administration of iodinated contrast agents (see PRECAUTIONS)
- Acute or chronic disease which may cause tissue hypoxia such as cardiac failure, recent myocardial infarction, respiratory failure, pulmonary embolism, shock, acute significant blood loss, sepsis, gangrene, pancreatitis.
- Elective major surgery (see PRECAUTIONS)
- Severe hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Lactation.

WARNINGS

Hypoglycaemia: Hypoglycaemia does not occur in patients receiving metformin hydrochloride alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulphonylureas) or ethanol.

Elderly, debilitated or malnourished patients and those with adrenal pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycaemic effects.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to a diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with metformin hydrochloride or sulphonylurea monotherapy, combined therapy with metformin hydrochloride and sulphonylurea may result in a response. Should secondary failure occur with combined metformin hydrochloride/sulphonylurea therapy, it may be necessary to initiate insulin therapy.

Metformin hydrochloride alone does not usually cause hypoglycaemia, although it may occur when metformin hydrochloride is used in conjunction with other antidiabetic agents (oral sulphonylureas, glinides, insulin). When initiating combination therapy, the risks of hypoglycaemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients.

PRECAUTIONS

Lactic acidosis:

Lactic acidosis is a rare but serious (high mortality in the absence of prompt treatment), metabolic complication, which can occur due to metformin accumulation during treatment with metformin. When it occurs, it is fatal in approximately 50% of cases. Lactic acidosis is a medical emergency and must be treated in hospital immediately. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications.

The incidence of lactic acidosis can and should be reduced by assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Special caution should be taken in the elderly due to the decrease of renal function with age.

The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases per 1000 patient years, with approximately 0.015 fatal cases per 1000 patient years). The onset is often subtle and accompanied by non-specific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. Lactic acidosis may also occur in association with a number of pathophysiological conditions, including diabetes mellitus, and when there is significant tissue hypoperfusion and hypoxaemia. Lactic acidosis is characterised by acidosis (decreased blood pH), elevated lactate levels with increased lactate/pyruvate ratio and electrolyte disturbances with increased anion gap.

Diagnosis
The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia. Lactic acidosis is characterised by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalised immediately (see **OVERDOSAGE - Treatment**).

Renal function:
As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels by using the Cockcroft-Gault formula) should be determined before initiating treatment and regularly thereafter:
- at least annually in patients with normal renal function,
- at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy, diuretic therapy or when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).

Surgery:

Metformin must be discontinued 48 hours before elective major surgery. Therapy may be restarted no earlier than 48 hours following surgery and only after renal function has been re-evaluated and found to be normal.

Heart failure:
Type 2 diabetic patients with heart failure are at an increased risk of hypoperfusion and possible renal insufficiency. Renal insufficiency is a risk factor for systemic accumulation of metformin and consequently lactic acidosis. Careful monitoring of renal function is recommended when metformin is used in patients with cardiac failure. The major risk of cardiac insufficiency is hypoxia.

When metformin is implicated as the cause of lactic acidosis, metformin plasma levels greater than 5 µg/mL are generally found (see PHARMACOKINETICS). Underlying renal disease, or deterioration in renal function, results in reduced clearance of metformin and drug accumulation and are therefore major risk factors in lactic acidosis.
The risk of lactic acidosis may therefore be significantly decreased by regular monitoring of renal function in patients taking metformin, patients taking concomitant diuretics and by the use of the minimum effective dose of metformin. In addition, metformin therapy should be temporarily stopped in the presence of any condition associated with hypoxaemia or dehydration, in patients suffering from serious infections or trauma (particularly if gastrointestinal disturbances are noted or acidosis is suspected) and in those undergoing surgery.

Impaired hepatic function:
Since impaired hepatic function has been associated with some cases or lactic acidosis, metformin should be avoided in patients with clinical or laboratory evidence of hepatic disease.

Administration of iodinated contrast agent
Radiological studies involving the use of intravascular iodinated contrast materials (for example intravenous urogram, intravenous cholangiography, angiography, any computed tomography scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore in patients with impaired renal function, metformin must be discontinued 48 hours before the test and in patients with normal renal function, metformin should be stopped at the time of the study and not recommended for 48 hours and only after renal function has been re-evaluated and found to be normal (see **Precautions - Interactions with other medicines**).

Other precautions:
All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
The usual laboratory tests for diabetes monitoring should be performed regularly.

Alcohol is known to potentiate the effects of metformin on lactate metabolism. Patients should therefore be warned against excessive alcohol intake, acute or chronic, while taking metformin.

Periodic assessment of renal, hepatic and cardiovascular function is recommended during prolonged periods of treatment with metformin.
Patients receiving continuous metformin therapy: It is recommended that serum vitamin B12 levels be measured prior to initiation treatment with metformin, after 6 months treatment and thereafter annually because of reports of decreased vitamin B12 absorption associated with metformin administration.

Use in the elderly
The risk of lactic acidosis, in association with metformin, is increased in elderly patients on long-term therapy due to the physiological alteration of the renal function and the possible accumulation of metformin. Metformin may be used in the elderly if contraindications and precautions are respected, the dosage is frequently reviewed and renal function monitored.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired.
Carcinogenesis, ,
Long term carcinogenicity studies have been performed in rats (dosing duration 104 weeks) and mice (dosing duration 91 weeks) at doses up to and including 900 and 1500 mg/kg/day respectively. These doses are approximately two to three times the recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly there was no tumorigenic potential observed with metformin in male rats. However an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day.

Genotoxicity
No evidence of a mutagenic potential of metformin was found in the Ames test (*S typhimurium*), gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), or *in vivo* micronuclei formation test (mouse bone marrow).

Impairment of Fertility
Fertility of male or female rats was unaffected by metformin administration at doses of up to 600 mg/kg/day, or approximately twice the maximum recommended daily dose on a body surface area basis.

Use in Pregnancy (Category C).

Australian Category C Definition: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

It is important to achieve strict normoglycaemia during pregnancy. Oral hypoglycaemic agents should be replaced by insulin.

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, any

decision to use this drug should be balanced against the benefits and risks. The safety of metformin in pregnant women has not been established.

Recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Oral hypoglycaemics may enter the fetal circulation and cause neonatal hypoglycaemia. There is a consensus among experts that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Use in Lactation
Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers, but caution should be exercised in such patients, and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Use
Metformin is not recommended for use in children except those with insulin resistant diabetes who are being treated in hospital.
The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated. No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially pre-pubescent children, is recommended.

INTERACTIONS WITH OTHER MEDICINES

Cimetidine: Reduced clearance of metformin has been reported during cimetidine therapy, so a dose reduction should be considered. Other cationic drugs such as amiloride, digoxin, morphine, procainamide, quinide, quinine, ranitidine, triamterene, trimethoprim, and vancomycin are eliminated by renal tubular secretion and theoretically have the potential to compete for common renal tubular transport systems with metformin. Careful patient monitoring is recommended in situations where cationic medications which are excreted via the proximal renal tubular secretory system are coadministered with metformin.

Anticoagulants: Metformin increased the elimination rate of vitamin K antagonists. Consequently, the prothrombin time should be closely monitored in patients in whom metformin and vitamin K antagonists are being coadministered. Cessation of metformin in patients receiving vitamin K antagonists can cause marked increases in the prothrombin time.

Nifedipine: A single dose metformin/nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of metformin and nifedipine increased plasma metformin C_{max} and AUC by 20% and 9% respectively, and increased the amount of metformin excreted in the urine. T_{max} and half-life of metformin were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin has minimal effects on the pharmacokinetics of nifedipine.

Sulphonylureas and meglitinides. During concomitant therapy with other antidiabetic agents, such as sulphonylureas or meglitinides, blood glucose should be monitored because combined therapy may cause hypoglycaemia.

Beta-blockers: Co administration of metformin and ßblockers may result in a potentiation of the anti–hyperglycaemic action. In addition, some of the premonitory signs of hypoglycaemia, in particular tachycardia may be masked. Monitoring of blood glucose should be undertaken during dosage adjustment of either agent.

ACE Inhibitors:
ACE-inhibitors may decrease the blood glucose levels. Therefore, dose adjustment of metformin hydrochloride may be necessary when such medicinal products are added or discontinued.

Calcium channel blockers: Calcium channel blockers may affect glucose control in diabetic patients; regular monitoring of glycaemic control is recommended.

Alcohol: Alcohol may make the signs of hypoglycaemia less clear and delayed hypoglycaemia may occur. The CNS depressant effects of alcohol plus hypoglycaemia can make driving or the operation of dangerous machinery much more hazardous. There is increased risk of lactic acidosis in acute alcohol intoxication, particularly with fasting, malnutrition or hepatic insufficiency.
Avoid consumption of alcohol and alcohol-containing medications.

Thiazide diuretics: Thiazide therapy may impair glucose tolerance. Dosage adjustment of metformin may be required.

Thyroid products: Thyroid products tend to produce hypoglycaemia and may lead to loss of control.

Combinations requiring precautions for use:
Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids and tetracosactides (systemic and local routes), beta-2-agonists, danazol, chlorpromazine at high dosages of 100 mg per day and diuretics:
More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon discontinuation.

Diuretics, especially loop diuretics:
May increase the risk of lactic acidosis due to their potential to decrease renal function.

Iodinated contrast media:
Metformin must be discontinued either 48 hours before the test when renal function is known to be impaired, or from the time of the test when renal function is known to be normal (see **Precautions - Administration of iodinated contrast materials**).

Other: Phenothiazines, oestrogens, oral contraceptives, phenytoin, nicotinic acid sympathomimetics and isoniazid tend to produce hyperglycaemia and patients receiving concomitant administration of any of these drugs with metformin hydrochloride should be closely observed to maintain glycaemic control.

Effects on laboratory tests
No information is available.

Effects on ability to drive or operate machinery
Patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (sulphonylureas, glinides, insulin).

ADVERSE EFFECTS

Gastrointestinal disorders
Very common: Mild gastrointestinal symptoms (such as diarrhoea, nausea, vomiting, abdominal pain and loss of appetite) are most frequent reactions to metformin (> 1/10), especially during the initial treatment period. These symptoms are generally transient and resolve spontaneously during continued treatment.

Gastrointestinal symptoms can possibly be avoided if metformin is taken with meals and the dose is increased slowly. Occasionally a temporary dose reduction can be considered. Occurrence of gastrointestinal symptoms, once a patient is stabilised on any dose of metformin could be due to lactic acidosis or other serious disease.

Metabolism and nutrition disorders
Very rare:
Lactic acidosis (see PRECAUTIONS) is a very rare (< 1/10 000) but serious metabolic complication that can occur due to metformin accumulation during treatment with metformin.

The onset of lactic acidosis is often subtle and accompanied by non-specific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrythmias with more marked acidosis. The patient and the patient's doctor should be instructed to notify the doctor immediately if they occur. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).

Lactic acidosis is a medical emergency that must be treated in hospital. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures should be instituted promptly.

A decrease of Vitamin B_{12} absorption with a decrease in serum levels has been observed in patients treated too long term with metformin, and appears to be generally without clinical significance (<1/10,000). Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia.

Therefore, serum B_{12} levels should be appropriately monitored or periodic parenteral B_{12} supplementation considered. (see Precautions)

Skin and subcutaneous tissue disorders
Very rare: Skin reactions such as mild erythema, pruritus and urticaria have been reported in some hypersensitive individuals, but the incidence is very rare. (< 1 /10 000).

Hepatobiliary Disorders
Very rare:
Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation, have been reported.

Nervous System Disorders
Common: Taste disturbance (3%) is common.

DOSAGE AND ADMINISTRATION

Life-threatening lactic acidosis can occur due to accumulation of metformin. Risk factors include renal impairment, old age and high doses of metformin above 2 g/day.

It is important that the tablets are taken in divided doses with meals. Initially 500 mg should be taken once or twice a day with breakfast and evening meal. If necessary the dose may be increased over a few weeks up to 1 g three times per day. The dose should be titrated with gradual dose increments until the desired effect is obtained.

500 mg three times a day is often sufficient to obtain a diabetic control. If necessary, the dose can be increased to 1 g three times daily, which is the maximum recommended daily dose. Control may be obtained within a few days but occasionally requires up to two weeks. Once control has been obtained, the dosage should be reviewed and reduced to the lowest maintenance level consistent with good diabetic control.

If dose titration has been achieved with one tablet strength, then the patient's response should be reassessed if a different strength or dose schedule is commenced.

Metformin dosage should be frequently reviewed in patients stabilised on metformin, especially if they develop an illness, as they may tolerate the drug less well, particularly if the illness is accompanied by a decrease in renal function. If necessary, metformin should be ceased for a few days during an illness and then restarted at low dosage, as for initial therapy. The action of metformin is progressive and no final assessment of the patient's real response should be made before the 21st day of treatment; blood sugar estimations are recommended during the initial 15 days of stabilisation. Metformin will not produce a hypoglycaemic state when used alone; however, due to its action in increasing insulin effectiveness, care must be taken when metformin is initially administered with parenteral doses of insulin.

Elderly: The initial maintenance dosing of metformin should be conservative in elderly patients, due to the potential for decreased renal function in this population. Any dosage

adjustment should be based on a careful assessment of renal function. Generally, elderly patients should not be titrated to the maximum dose of metformin.

Debilitated patients: In debilitated or malnourished patients, the dosing should be conservative and based on careful assessment of renal function.

OVERDOSAGE

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

Symptoms

Hypoglycaemia has not been seen with ingestion of up to 85 g of metformin alone, although lactic acidosis has occurred in such circumstances. The onset of lactic acidosis is often subtle and accompanied only by non-specific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrythmias with more marked acidosis. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis, such as ketonuria and ketonaemia.

Treatment

Lactic acidosis should be feared in diabetic metformin treated patients with overdose. Lactic acidosis is diagnosed and monitored by measuring serum electrolytes, arterial pH and p_{CO2} and arterial lactate plasma level.

The aim of treatment is to manage any underlying disorder and in some cases this will be sufficient to enable the body's homeostatic mechanism to correct the acid-base imbalance. The advantages of more active treatment of the acidosis must be balanced against the risks, including over-alkalinisation with sodium bicarbonate. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good haemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

PRESENTATION AND STORAGE CONDITIONS

Metformin Sandoz tablets 500 mg: white, film coated, biconvex capsule shaped tablet with central breakline on one side and 500 embossed on the other side. 100's in blisters and bottles.
Metformin Sandoz tablets 850 mg: white, film coated, round, biconvex tablet plain on one side and '850' embossed on the other side. 60's in blisters and bottles.

Store below 25°C.

POISON SCHEDULE

S4 –Prescription Only Medicine

NAME AND ADDRESS OF SPONSOR

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Tel: 1800 634 500

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 02/02/2010

DATE OF MOST RECENT AMENDMENT: 13/04/2016