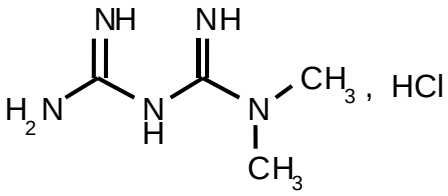
APO-METFORMIN 500 TABLETS
APO-METFORMIN 850 TABLETS
APO-METFORMIN 1000 TABLETS

NAME OF THE MEDICINE

Metformin hydrochloride.

Chemical Name: 1,1-dimethylbiguanide hydrochloride

Structural Formula:



Molecular Formula: $C_4H_{11}N_5.HCl$

Molecular Weight: 165.6

CAS Registry No: 1115-70-4

DESCRIPTION

Metformin hydrochloride is a white, crystalline powder which is almost odourless and hygroscopic. It is freely soluble in water, slightly soluble in ethanol (96%) and practically insoluble in chloroform and in ether.

PHARMACOLOGY

Metformin is an oral biguanide hypoglycaemic agent. It 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 an increase of insulin sensitivity. It does not stimulate insulin release but does require the presence of insulin to exert its anti-hyperglycaemic 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 lowers both basal and post-prandial blood glucose in diabetic patients but does not cause hypoglycaemia in either diabetics or normal individuals.

Pharmacokinetics

Absorption

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 of meformin rather than an increase in elimination. After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are non-linear.

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 µg/mL. During controlled clinical trials, maximum metformin plasma levels did not generally exceed 5 µg/mL, even at maximum doses.

Distribution

Metformin is not bound to plasma proteins.

Metabolism

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

Excretion

In patients with significantly 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.

Paediatrics

Following an oral dose, children 12 years and older, have shown similar pharmacokinetic profile of metformin to that observed in adults. Pharmacokinetic data in children between 10 and 12 years are not available.

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:

- 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 sulfonylurea 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 sulfonylurea 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 sulfonylurea, 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 fully established.

Paediatrics

In a double-blind, placebo-controlled study in 82 paediatric patients aged 10 to 16 years with type 2 diabetes (mean FPG 10.1 mmol/L), treatment with metformin (up to 2000 mg/day) for up to 16 weeks (mean duration of treatment 11 weeks) resulted in a significant mean net reduction in FPG of 3.6 mmol/L, compared with placebo.

INDICATIONS

Metformin is indicated in the treatment of type 2 diabetes mellitus in adults, children from 10 years of age and adolescents, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

For adult patients, metformin may be used as initial treatment or in sulfonylurea failures either alone or in combination with a sulfonylurea and other oral agents or as adjuvant therapy in insulin requiring type 2 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.
- APO-Metformin 500/850/1000 should not be given to patients who have experienced hypersensitivity to the product or any of its ingredients.
- Hypersensitivity to biguanides.
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (creatinine clearance < 60 mL/min).
- 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.

Risk of Lactic Acidosis

Because of the danger of lactic acidosis, metformin should not be used in the presence of the following conditions: diminished renal function; cardiovascular disease (e.g. coronary insufficiency, myocardial infarction, and hypertension); conditions which may be associated with tissue hypoxia (e.g. gangrene, circulatory shock, acute significant blood loss); pulmonary embolism; severe hepatic dysfunction; pancreatitis; excessive alcohol intake; concomitant use of diuretics.

PRECAUTIONS

Lactic acidosis is a rare but serious metabolic complication which can occur due to accumulation of metformin during treatment. 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. 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, myalgias, 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 an increased anion gap.

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 PHARMACOLOGY, Pharmacokinetics). Underlying renal disease, or a deterioration in renal function, result 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 and those patients on concomitant diuretics. The use of minimum effective dose of metformin is recommended. 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.

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 normal renal function, metformin should be stopped at the time of the study and not recommenced for 48 hours and only after renal function has been re-evaluated and found to be normal.

Surgery

Metformin hydrochloride 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.

Other Precautions

- Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should; therefore, be warned against excessive alcohol intake, acute or chronic, while taking metformin.
- 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.
- Periodic assessment of renal, hepatic and cardiovascular function is recommended during prolonged periods of treatment with metformin.
- Metformin hydrochloride alone does not cause hypoglycaemia; however, caution is advised when it is used in combination with other antidiabetic agents (sulphonylureas, glinides, insulin).
- In patients receiving continuous metformin therapy, it is recommended that serum vitamin B_{12} levels be measured prior to initiation treatment with metformin, after 6 months treatment and thereafter annually because of reports of decreased vitamin B_{12} absorption associated with metformin administration.

Carcinogenicity/Mutagenicity

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. Three doses are both 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 tumourigenic 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.

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

Fertility of male or female rats was unaffected by metformin administration at doses 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)

Oral hypoglycaemics may enter the foetal circulation and cause neonatal hypoglycaemia. It is important to achieve strict normoglycaemia during pregnancy. Oral anti-hyperglycaemic 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 foetal 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.

Because information available suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, 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.

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.

Use in Children

Metformin is not recommended for use in children under 10 years of age.

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 clinical data in relation to the long-term effect of metformin on the development of skeletal and reproductive system in children and adolescents are not 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

Pharmacokinetic Interactions

Cimetidine

Co-administration of cimetidine with metformin may lead to reduced renal clearance of metformin and hence increased plasma metformin concentrations. Dose reductions should therefore be considered in patients being treated with cimetidine.

Anticoagulants

Metformin increases 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 co-administered. 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.

Pharmacodynamic Interactions

Sulfonylureas & Repaglinide

During concomitant therapy with either sulfonylureas or repaginide, blood glucose should be monitored because combined therapy may cause hypoglycaemia.

Other Hypoglycaemics

During combined therapy of metformin with other hypoglycaemics, blood glucose should be monitored because of the possibility of hypoglycaemia.

Beta-Blockers

Co-administration of metformin and beta-blockers 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

Co-administration of metformin and ACE inhibitors may result in a potentiation of the hypoglycaemic action. Monitoring of blood glucose should be undertaken during dosage adjustment of either agent.

Calcium Channel Blockers

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

Alcohol

The risk of lactic acidosis increases with acute intoxication, particularly in cases of fasting or malnutrition and hepatic insufficiency. Alcohol may make the signs of hypoglycaemia less clear, and delayed hypoglycaemia can occur. The CNS depressant effects of alcohol plus hypoglycaemia can make driving and operation of dangerous machinery much more hazardous.

Thiazide Diuretics

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

Thyroid Products

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

Glucocoritcoids (Systemic and Local Routes), Beta-2-Antagonists & Diuretics

Glucocorticoids (systemic and local routes), beta-2-antagonists and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the anti-diabetic medicinal product during therapy with the other medicinal product and upon its discontinuation.

Iodinated Contrast Media

Metformin should be temporarily withheld in patients undergoing radiological studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function (see **PRECAUTIONS**).

Effects on Laboratory Tests

No information is available.

Effects on ability to drive or operate machinery

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machinery. However, 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

Very Common

Mild gastrointestinal symptoms (such as diarrhoea, nausea, vomiting, abdominal pain and loss of appetite) are the 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 side effects can possibly be avoided if metformin is taken with meals and if 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.

Systemic / Metabolic

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 bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Lactic acidosis should be suspected in any diabetic patient with a 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 promptly instituted.

Nervous System Disorders

Common

Taste disturbance (3%) is common.

Dermatological

Very Rare

Skin reactions such as erythema, pruritus and urticaria have been reported, but the incidence is rare (< 1/10,000).

Haematological

Very Rare

A decrease in vitamin B_{12} absorption with a decrease in serum levels has been observed in patients treated long-term with metformin (< 1/10,000). Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia. Therefore, serum B_{12} levels should be appropriately monitored and periodic parenteral B_{12} supplementation considered.

Hepatobiliary Disorders

Isolated Reports

Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation, have been reported.

In clinical trials in children and adolescents with type 2 diabetes, the profile of adverse reactions was similar to that observed in adults.

DOSAGE AND ADMINISTRATION

Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment; other risk factors include old age associated with reduced renal function and high doses of metformin above 2 g per 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 and if necessary 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 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 attained 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.

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 and 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.

Use in Children and Adolescents

Metformin can be used as monotherapy in children from 10 years of age and adolescents. The usual starting dose is one tablet of 500 mg or 850 mg once daily, given during meals or after meals.

After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability.

The maximum recommended dose of metformin is 2 g daily, taken as two or three divided doses.

In Debilitated or Malnourished Patients

The dosing should be conservative and based on a careful assessment of renal function.

OVERDOSAGE

Symptoms

Hypoglycaemia has not been seen with ingestion of up to 85 g of metformin alone, although lactic acidosis has occurred in such circumstances. This disorder is a medical emergency and must be treated in hospital. 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 bradyarrhythmias with more marked acidosis. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).

Treatment

Lactic acidosis may develop in diabetic metformin-treated patients with overdose. Lactic acidosis is diagnosed and monitored by measurement of serum electrolytes, arterial pH and pCO_2 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 hydrochoride is dialysable (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.

Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

APO-Metformin 500 Tablets: White coloured, film-coated biconvex capsule shaped tablet with central breakline on one side and '500' embossed on the other side.

Blister packs of 100 tablets: AUST R 174815.

APO-Metformin 850 Tablets: White coloured, film-coated, round biconvex tablets plain on one side and '850' embossed on the other side.

Blister packs of 60 tablets: AUST R 174816.

APO-Metformin 1000 Tablets: White, film-coated, capsule-shaped, biconvex tablet, plain on one side and a breakline on the other.

Blister packs of 10, 30 60 and 90 tablets: AUST R 176509.

APO-Metformin 500/850/1000 tablets are intended for oral administration. Each tablet contains 500 mg, 850 mg or 1000 mg metformin hydrochloride, as the active ingredient. In addition, each tablet contains the following inactive ingredients: hypromellose, macrogol 6000, magnesium stearate, povidone, propylene glycol, silica – colloidal anhydrous, sodium starch glycollate, starch – maize, talc – purified and titanium dioxide.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 : Prescription Only Medicine.

Date of TGA approval: 8 November 2010

Date of most recent amendment: 13 May 2013