CHEMMART METFORMIN XR (500 & 1000) TABLETS

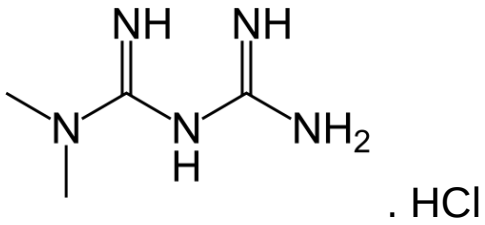
Life-threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment; other risk factors include old age associated with reduced renal function and high doses of metformin hydrochloride (≥ 2 g per day).

NAME OF THE MEDICINE

Metformin hydrochloride.

Chemical Name: 1,1-dimethylbiguanide hydrochloride

Structural Formula:



Molecular Formula: $C_4H_{12}ClN_5$

Molecular Weight: 165.62

CAS Registry Number: 1115-70-4

DESCRIPTION

White crystals easily soluble in water, sparingly soluble in alcohol and practically insoluble in acetone and methylene chloride.

Metformin is a strong base with a pKa greater than 12. At pH < 12, which is always the case in the body, metformin is very hydrophilic: the octanol/water partition coefficient is 0.05. The melting point of metformin hydrochloride is 224°C. Metformin hydrochloride is a very stable molecule.

Each modified release tablet contains either 500 mg or 1000 mg metformin hydrochloride (HCl). The tablets also contain the following excipients: hypromellose, povidone, colloidal anhydrous silica and magnesium stearate.

Tablet shells may be present in the faeces (see **PRECAUTIONS, Other Precautions**).

PHARMACOLOGY

Pharmacodynamics

Metformin is an oral hypoglycaemic agent; it is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

- Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- Delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters.

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term and long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Pharmacokinetics

Absorption

At steady state, similar to the immediate release formulation, C_{max} and AUC do not increase in proportion with the administered dose. The administration of two, three, or four tablets 500 mg modified release tablets results in a 1.8-, 2.4- and 3.0-fold increase for C_{max} and a 2.0-, 2.7- and 3.2-fold increase in AUC.

Intrasubject variability of C_{max} and AUC of metformin modified release tablets is comparable to that observed with metformin immediate release tablets.

No accumulation is observed after repeated administration of up to 2000 mg metformin hydrochloride as modified release tablets (administered as four 500 mg modified release tablets).

Metformin absorption from the modified release formulation is not altered by meal composition.

Pharmacokinetic parameters, from healthy volunteers, for **this medicine**, are presented below.

After an oral dose of the 500 mg modified release tablet, under fasted conditions, metformin absorption is slightly delayed compared to an immediate release tablet; delay is approximately an hour (t_{max} for the modified release tablet is 3½ hours and t_{max} for the immediate release tablet is 2½ hours).

AUC is decreased by ~35% when the modified release tablet is administered under fasted conditions compared to fed, C_{max} is unaffected and the t_{max} is reduced by 1–2 hours.

Cross-study comparison of Metformin XR 500 and Metformin XR 1000			
Dose (± food)	**Median t_{max} (range) [h]**	**Mean C_{max} [ng/mL]**	**Mean $AUC_{0-\infty}$ [ng*h/mL]**
500 mg steady state (fasted)	3.5 (2.0 – 5.0)	686.8	5,007.6*
500 mg single dose (fasted)	4.0 (2.0 – 6.0)	635.3	5,013.5
500 mg single dose (fed)	6.0 (4.5 – 9.0)	618.8	7,968.1
1000 mg single dose (fasted)	3.5 (1.5 – 4.5)	1,051.7	8,242.5
1000 mg single dose (fed)	4.5 (4.0 – 10.0)	1,072.6	12,539.7
1000 mg steady state (fed)	5.0 (4.5 – 10.3)	1,243.7	14,679.7*

* = AUC_{τ}

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution V_d ranged 63–276 L.

Metabolism

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Excretion

Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6½ hours. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

CLINICAL TRIALS

Metformin HCl modified release tablet has been evaluated in three double-blind, randomized, multicentre, parallel-group clinical trials, two of which employed a placebo control. These studies were each followed by a 52-week open-label extension study involving subjects who completed double-blind treatment and/or were withdrawn for inadequate glycaemic control. The primary endpoint was the mean change in HbA_{1C} from baseline in each case.

Both placebo-controlled studies were in diet-failed patients previously not exposed to metformin. One study evaluated once-daily metformin HCl modified release tablet at daily doses of 500 mg, 2 × 500 mg, 3 × 500 mg and 4 × 500 mg, and also twice-daily 2 × 500 mg, for 16 weeks. Treatment with once-daily metformin HCl modified release tablet resulted in dose-related reductions in indices of glycaemic control (HbA_{1C}, fasting plasma glucose and the proportions of patients achieving HbA_{1C} < 7.0% at study end or last prior measurement) that were significant at all doses relative to placebo (Table 1). The results of a 52-week open-label extension to this study (Table 1) showed that the anti-hyperglycaemic effects of metformin HCl modified release tablet were maintained over time. There was no weight gain in any treatment group.

Table 1. Placebo-controlled dose-ranging evaluation of metformin HCl modified release tablet in diet-failed patients (double-blind 16 weeks; open-label 52 weeks)

	Double-blind: Placebo	**Double-blind: Metformin HCl modified release tablet**					**Open-label: Metformin HCl modified release tablet 1000 mg once daily**
		500 mg once daily	**1000 mg once daily**	**1500 mg once daily**	**2000 mg once daily**	**1000 mg twice daily**	
Haemoglobin A1c	n = 111	n = 115	n = 115	n = 111	n = 125	n = 112	n = 404
Baseline Mean (%)	8.4	8.2	8.4	8.3	8.4	8.4	8.1
Final Mean (%)	8.5	7.8	7.8	7.5	7.5	7.3	7.1
Difference from placebo/baseline[a]	–	-0.6*	-0.7*	-1.0*	-1.0*	-1.2*	-1.0
Fasting Plasma Glucose	n = 113	n = 126	n = 118	n = 120	n = 132	n = 122	n = 387
Baseline Mean (mmol/L)	10.0	10.1	10.2	9.9	10.0	10.1	9.5
Final Mean (mmol/L)	10.4	9.3	9.1	8.4	8.4	8.2	7.9
Difference from placebo/baseline[a]	–	-1.3*	-1.5*	-2.0*	-2.1*	-2.3*	-1.5
Body Weight Mean Change from baseline (kg)	-0.8	-0.6	-0.6	-0.3	-0.7	-1.0	-1.2
Final HBA_{1c} Distribution	n = 111	n = 115	n = 115	n = 111	n = 126	n = 112	n = 404
< 7% (%)	11	18	23†	38*	45*	50*	47
≥ 7% (%)	89	82	77	62	55	50	53

† p<0.05; * p< 0.001 vs. placebo (statistical evaluation for double-blind study only).
[a] difference from placebo for double-blind studies and difference from baseline for the open-label study.

The second placebo-controlled study evaluated metformin HCl modified release tablet at a target dose of 2 × 500 mg once-daily for a period of 12 weeks. Indices of glycaemic control (as above) improved significantly compared with placebo (Table 2). The magnitudes of improvements were comparable to those observed in the dose-ranging study (Table 1). The accompanying 52-week open-label study again showed that improvements in glycaemia were durable over time. No weight gain was associated with metformin HCl modified release tablet treatment.

Table 2. Placebo-controlled evaluation of metformin HCl modified release tablet in diet-failed patients (double-blind 12 weeks; open-label 52 weeks)

	Double-blind:		Open-label:
	Placebo	**Metformin HCl modified release tablet 1000 mg once daily**	**Metformin HCl modified release tablet**
Haemoglobin A1c	n = 79	n = 155	n = 59
Baseline Mean (%)	7.9	8.0	7.7
Final Mean (%)	8.0	7.5	7.2
Difference from placebo/baseline[a]	-	-0.6*	-0.6
Fasting Plasma Glucose	n = 79	n = 159	n = 57
Baseline Mean (mmol/L)	9.6	9.9	9.2
Final Mean (mmol/L)	9.6	8.6	8.7
Difference from placebo/baseline[a]	–	-1.2*	-0.5
Body Weight Mean Change from Baseline (kg)	-0.8	-0.3	-0.4
Final HBA1c Distribution	n = 79	n = 155	n = 59
< 7% (%)	11	45†	44
≥ 7% (%)	89	55	56

† p<0.05; * p< 0.001 vs. placebo (statistical evaluation for double-blind study only).
[a] difference from placebo for double-blind studies and difference from baseline for the open-label study.

The third randomized, double-blind study evaluated the effects of switching from the immediate-release formulation of metformin HCl to metformin HCl modified release tablet. Patients sub-optimally controlled with metformin received immediate-release metformin HCl 500 mg twice daily, were randomized to continue on immediate-release metformin HCl or to receive once-daily metformin HCl modified release tablet at a dose of 2 × 500 mg or 3 × 500 mg, for a period of 12 weeks. Indices of glycaemia were not markedly altered after switching between the formulations, either in the double-blind study or an associated 52-week open-label study (Table 3).

Table 3. Double-blind, randomized study evaluating the effects of a switch from immediate-release metformin HCl to metformin HCl modified release tablet

	Double-blind:			Open-label:
	Metformin HCl immediate-release tablet 500 mg twice daily	**Metformin HCl modified release tablet 1000 mg once daily**	**Metformin HCl modified release tablet 1500 mg once daily**	**Metformin HCl modified release tablet**
Haemoglobin A_{1c}	n = 66	n = 70	n = 65	n = 112
Baseline Mean (%)	7.0	7.0	7.0	6.9
Final Mean	7.1	7.2	7.1	7.1
Mean change	0.2	0.2	0.04	0.2
Fasting Plasma Glucose	n = 69	n = 72	n = 70	n = 109
Baseline Mean (mmol/L)	7.1	7.3	7.3	7.0
Final Mean (mmol/L)	7.8	7.8	7.5	7.5
Mean change	0.7	0.5	0.2	0.5
Final HBA_{1c} Distribution	n = 66	n = 70	n = 65	n = 112
< 7% (%)	47	43	49	48
≥ 7% (%)	53	57	51	52

The prospective randomized study (UKPDS) has established the long-term benefit of intensive blood glucose control in overweight type 2 diabetes. The immediate release tablet form of metformin was used in the UKPDS.

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 a 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 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 monotherapy or in combination with other oral hypoglycaemic agents, or with insulin.

CONTRAINDICATIONS

- Hypersensitivity to metformin or to any of the excipients
- 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, Administration of Iodinated Contrast Materials**)
- 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
- Major surgery (see **PRECAUTIONS, Surgery**)
- Severe hepatic insufficiency, acute alcohol intoxication, alcoholism
- Lactation (see **PRECAUTIONS, Use in Lactation**).

PRECAUTIONS

Lactic Acidosis

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. 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.

Diagnosis

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders such 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, it is recommended that creatinine clearance and/or serum creatinine levels be determined before initiating treatment and regularly thereafter:

- At least annually in patients with normal renal function;
- At least 2–4 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 or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).

Administration of Iodinated Contrast Materials

The intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure. This may induce metformin accumulation and may expose the patient to lactic acidosis. Therefore, 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. It should not be reinstituted until 48 hours after the test and only after renal function has been re-evaluated and found to be normal (see **CONTRAINDICATIONS** and **INTERACTIONS WITH OTHER MEDICINES**).

Surgery

Metformin must be discontinued 48 hours before elective 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

- 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.
- Metformin alone does not cause hypoglycaemia; however, caution is advised when it is used in combination with other hypoglycaemic agents (sulfonylureas, glitinides, insulin).
- The tablet shells may be present in the faeces. Patients should be advised that this is normal.

Use in Pregnancy (Category C)

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

To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development.

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

Use in Lactation

Metformin is excreted into milk in lactating rats. Similar data are not available in humans and a decision should be made whether to discontinue breast feeding or to discontinue metformin, taking into account the importance of the medicinal product to the mother.

Paediatric Use

In absence of available data, metformin HCl modified release tablets should not be used in children.

Genotoxicity

Preclinical data reveal no specific hazard for humans based on conventional studies on genotoxicity.

Carcinogenicity

Preclinical data reveal no specific hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, carcinogenic potential or reproductive toxicity.

Effect on Ability to Drive and Use 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 hypoglycaemic agents (sulfonylureas, glitinides, insulin).

INTERACTIONS WITH OTHER MEDICINES

Contraindicated Combination

Iodinated Contrast Materials

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. It should not be reinstituted until 48 hours after the test and only after renal function has been re-evaluated and found to be normal (see **CONTRAINDICATIONS** and **PRECAUTIONS, Administration of Iodinated Contrast Materials**).

Inadvisable Combination

Alcohol

Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:

- Fasting or malnutrition;
- Hepatic insufficiency.

Avoid consumption of alcohol and alcohol-containing medications.

Combinations Requiring Precautions for Use

Medicines with Intrinsic Hyperglycaemic Activity

[e.g. glucocorticoids, thyroid products and tetracosactides (systemic and local routes), β_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.

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.

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.

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.

Calcium Channel Blockers

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

Cimetidine

Reduced clearance of metformin has been reported during cimetidine therapy, so a dose reduction should be considered.

Diuretics, especially Loop Diuretics

May increase the risk of lactic acidosis due to their potential to decrease renal function.

Hypoglycaemic Agents

Metformin alone does not cause hypoglycaemia; however, caution is advised when it is used in combination with other hypoglycaemic agents (sulfonylureas, glitinides, insulin).

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 had minimal effects on the pharmacokinetics of nifedipine.

Thyrotropin

Reduction of thyrotropin (TSH) serum levels has been reported in diabetic patients with hypothyroidism when metformin therapy is initiated.

ADVERSE EFFECTS

In post-marketing data and in controlled clinical studies, adverse event reporting in patients treated with metformin HCl modified release tablets (containing metformin 500 mg, 750 mg or 1000 mg) was similar in nature and severity to that reported in patients treated with metformin immediate release tablets.

The following undesirable effects may occur under treatment with metformin. Frequencies are defined as follows:

- very common - > 1/10
- common - ≥ 1/100, <1/10
- uncommon - ≥ 1/1,000, <1/100
- rare - ≥ 1/10,000, <1/1,000
- very rare - < 1/10,000
- not known - (cannot be estimated from the available data).

Within each frequency grouping, adverse effects are presented in order of decreasing seriousness.

Gastrointestinal Disorders

Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. A slow increase of the dose may improve gastrointestinal tolerability.

Hepatobiliary Disorders

Not Known: Isolated reports of liver function test abnormalities or hepatitis resolving upon metformin discontinuation.

Metabolism and Nutrition Disorders

Uncommon: Decrease of vitamin B_{12} absorption with a decrease of serum levels during long-term use of metformin has been observed in patients treated long-term with metformin. Consideration of such 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.

Very rare: Lactic acidosis (see **PRECAUTIONS**).

Not known: Reduction of thyrotropin (TSH) serum levels has been reported in diabetic patients with hypothyroidism when metformin therapy is initiated.

Nervous System Disorders

Common: Taste disturbance.

Skin and Subcutaneous Tissue Disorders

Very rare: Skin reactions such as erythema, pruritus, urticaria.

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 HCl (≥ 2 g per day).

Monotherapy and Combination with other Oral Hypoglycaemic Agents

Initiating Therapy with Metformin XR

For patients new to metformin, the usual starting dose is one Metformin XR 500 tablet, once daily, with the evening meal. If the starting dose requires 750 mg modified release metformin HCl, then alternative brands will be required, as Metformin XR 500 cannot be divided.

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

Dosage increases should be made in increments of 500 mg every 10–15 days, up to a maximum of 2000 mg once daily with the evening meal. If the dosage increases require 750 mg modified release metformin HCl, then alternative brands will be required, as Metformin XR 500 cannot be divided.

Combining Different Metformin XR Dosage Strengths

The combined use of different strengths of Metformin XR 500 and Metformin XR 1000 is not recommended – only one strength should be used at a time in order to avoid accidentally exceeding the recommended upper daily dose limit of 2000 mg.

Maintenance Therapy with Metformin XR

Metformin XR 1000 is intended as a maintenance therapy for patients currently treated with either 1000 mg or 2000 mg metformin HCl. In patients already treated with metformin HCl immediate release tablets, the starting dose of metformin HCl modified release tablets should be equivalent to the daily dose of metformin HCl immediate release tablets.

The maximum recommended dose is four tablets of Metformin XR 500 or two tablets of 750mg modified release metformin HCl (alternative brands) or two tablets of Metformin XR 1000, once daily, with the evening meal.

Switching from Metformin XR to immediate release metformin

If glycaemic control is not achieved with the maximum recommended dose of four Metformin XR 500 tablets or two tablets of 750mg modified release metformin HCl (alternative brands) or two Metformin XR 1000 tablets, patients may be switched to metformin HCl immediate release tablets to a maximum dose of 3000 mg daily.

Switching from immediate release metformin to Metformin XR

In patients already treated with metformin HCl immediate release tablets, the starting dose of Metformin XR 500 or Metformin XR 1000 should be equivalent to the daily dose of metformin HCl immediate release tablets. In patients treated with immediate release metformin HCl at a dose above 2000 mg daily, switching to Metformin XR 500 or MetforminXR 1000 is not recommended.

Transferring from other oral hypoglycaemic agents

If transfer from another oral hypoglycaemic agent is intended, discontinue the other agent. Initiate with one Metformin XR 500 tablet, once daily, with the evening meal and titrate as described under "Initiating therapy with Metformin XR".

Combination with Insulin

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose is one Metformin XR 500 tablet, once daily, with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements. If the starting dose requires 750 mg modified release metformin HCl, then alternative brands will be required, as Metformin XR 500 cannot be divided. After titration, switching to Metformin XR 1000 should be considered.

Elderly

Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary.

Children

In absence of available data, Metformin XR 500 or Metformin XR 1000 should not be used in children.

OVERDOSAGE

Symptoms

Although hypoglycaemia has not been seen with ingestion of up to 85 g of metformin alone, 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 also 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 levels.

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-alkalinization with sodium bicarbonate. As metformin 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 Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Chemmart Metformin XR 500

Each modified release tablet contains 500 mg metformin hydrochloride and is intended for oral administration.

White, capsule shaped uncoated tablet with XR 500 on one side and a plain on the other side
Blister pack (PVC/Al) of 120 tablets: AUST R 278178.

Chemmart Metformin XR 1000

Each modified release tablet contains 1000 mg metformin hydrochloride and is intended for oral administration.

White capsule shaped uncoated tablet with XR 1000 one side and a plain on the other side.

Blister pack (PVC/Al) of 60 tablets: AUST R 278177.

Not all strengths may be marketed.

Storage

Store in Original Container, Store below 25°C.

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG) 26 August 2016

DATE OF MOST RECENT AMENDMENT