For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

AZUKON-M
(GLICLAZIDE AND METFORMIN TABLETS)

COMPOSITION:
Each uncoated tablet contains:
Gliclazide I.P. 80 mg
Metformin Hydrochloride I.P. 500 mg

Therapeutic indications
For the treatment of non-insulin dependent diabetes (type-II) in adult patients where single drug therapy, diet and exercise do not result in adequate glycaemic control.

POSOLOGY AND METHOD OF ADMINISTRATION
Adults: The final dosage regimen depends on the individual requirements of the patient and is at the direction of the physician. The usual starting dose of AZUKON-M is 2 tablets per day with meals, 1 tablet with breakfast and 1 tablet with dinner. The dose can be increased according to the severity of the disease. Patients can also be titrated from 1 tablet twice a day to 2 tablets twice a day after 2 weeks.

Elderly: Plasma clearance of Gliclazide is not altered in the elderly and steady state plasma levels can therefore be expected to be similar to those in adults under 65 years. Clinical experience in the elderly to date shows that Gliclazide is effective and well tolerated. Care should be exercised however, when prescribing sulphonylureas in the elderly due to a possible age-related increased risk of hypoglycemia. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with Impaired renal function, AZUKON-M should only be used in patients with normal renal function. Because aging is associated with reduced renal function, AZUKON-M should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function.

CONTRAINDICATIONS
- Hypersensitivity to drug or any of the excipients
- Diabetic ketoacidosis, diabetic pre-coma.
- Moderate (stage 3b) and severe renal failure or renal dysfunction (CrCl < 45 ml/min or eGFR < 45 ml/min/1.73m^2).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- treatment with miconazole
- lactation

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Metformin

Lactic acidosis

Lactic acidosis is a very rare, but serious (high mortality rate 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 impaired renal failure or acute worsening of renal function. Special caution should be paid to situations where renal function may become impaired, for example in case of dehydration (severe diarrhoea or vomiting), or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). In the acute conditions listed, metformin should be temporarily discontinued.

Other associated risk factors should be considered to avoid lactic acidosis such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia (such as decompensated cardiac failure, acute myocardial infarction)

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps, digestive disorders as abdominal pain and severe asthenia. Patients should be instructed to notify these signs immediately to their physicians if they occur, notably if patients had a good tolerance to metformin before. Metformin should be discontinued, at least temporarily, until the situation is clarified. Reintroduction of metformin should then be discussed taking into account the benefit/risk ratio in an individual basis as well as renal function.

Diagnosis:

Lactic acidosis is characterised by acidotic dyspnoea, 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. In case of lactic acidosis, the patient should be hospitalised immediately.

Physicians should alert the patients on the risk and on the symptoms of lactic acidosis.

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) or eGFR 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 creatinine clearance at the lower limit of normal and in elderly subjects.

In case CrCl is <45 ml/min (eGFR < 45 ml/min/1.73m^2), metformin is contraindicated

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 in case of dehydration, or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).

In these cases, it is also recommended to check renal function before initiating treatment with metformin.

Cardiac function
Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, metformin is contraindicated.

Administration of iodinated contrast media
The intravascular administration of iodinated contrast media in radiologic studies can lead to renal failure. This may induce metformin accumulation and may increase the risk for lactic acidosis. In patients with eGFR > 60 ml/min/1.73 m^2, metformin must be discontinued prior to, or at the time of the test and not be reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further.

In patients with moderate renal impairment (eGFR between 45 and 60 ml/min/1.73m^2), metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.

Surgery
Metformin must be discontinued 48 hours before elective surgery under general, spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

Paediatric population
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 prepubescent children, is recommended.

Children aged between 10 and 12 years
Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of metformin in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

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, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

Gliclazide

Hypoglycaemia***:***

This treatment should be prescribed only if the patient is likely to have a regular food intake (including breakfast). It is important to have a regular carbohydrate intake due to the increased risk of hypoglycaemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Hypoglycaemia is more likely to occur during low-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycaemic agents is being used.

Hypoglycaemia may occur following administration of sulfonylureas

Some cases may be severe and prolonged. Hospitalisation may be necessary and glucose administration may need to be continued for several days.

Careful selection of patients, of the dose used, and clear patient directions are necessary to reduce the risk of hypoglycaemic episodes.

Factors which increase the risk of hypoglycaemia:

• Patient refuses or (particularly in elderly subjects) is unable to co-operate,
• Malnutrition, irregular mealtimes, skipping meals, periods of fasting or dietary changes,
• Imbalance between physical exercise and carbohydrate intake,
• Renal insufficiency,
• Severe hepatic insufficiency,
• Certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency,
• Concomitant administration of certain other medicines

Renal and hepatic insufficiency: the pharmacokinetics and/or pharmacodynamics of gliclazide may be altered in patients with hepatic insufficiency or severe renal failure. A hypoglycaemic episode occurring in these patients may be prolonged, so appropriate management should be initiated.

Patient information: the risks of hypoglycaemia, together with its symptoms treatment, and conditions that predispose to its development, should be explained to the patient and to family members.

The patient should be informed of the importance of following dietary advice, of taking regular exercise, and of regular monitoring of blood glucose levels.

Poor blood glucose control: blood glucose control in a patient receiving antidiabetic treatment may be affected by any of the following: fever, trauma, infection or surgical intervention. In some cases, it may be necessary to administer insulin.

The hypoglycaemic efficacy of any oral antidiabetic agent, including gliclazide, is attenuated over time in many patients: this may be due to progression in the severity of the diabetes, or to a reduced response to treatment. This phenomenon is known as secondary failure which is distinct from primary failure, when an active substance is ineffective as first-line treatment. Adequate dose adjustment and dietary compliance should be considered before classifying the patient as secondary failure.

Laboratory tests: Measurement of glycated haemoglobin levels (or fasting venous plasma glucose) is recommended in assessing blood glucose control. Blood glucose self-monitoring may also be useful.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since gliclazide belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

DRUG INTERACTION
Metformin
Concomitant use not recommended
Alcohol
Acute alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting or malnutrition, hepatic insufficiency.

Avoid consumption of alcohol and alcohol-containing medicinal product.

Iodinated contrast media
Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and an increased risk of lactic acidosis.

In patients with eGFR > 60 ml/min/1.73m^2,metformin must be discontinued prior to, or at the time of the test and not be reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further.

In patients with moderate renal impairment (eGFR between 45 and 60 ml/min/1.73m^2), metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.

Combinations requiring precautions for use
Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics)
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 its discontinuation.

Diuretics, especially loop diuretics
They may increase the risk of lactic acidosis due to their potential to decrease renal function.
Gliclazide
The following products are likely to increase the risk of hypoglycaemia
Contra-indicated combination
• **Miconazole** (systemic route, oromucosal gel): increases the hypoglycaemic effect with possible onset of hypoglycaemic symptoms, or even coma.

Combinations which are not recommended

• **Phenylbutazone** (systemic route): increases the hypoglycaemic effect of sulfonylureas (displaces their binding to plasma proteins and/or reduces their elimination).

It is preferable to use a different anti-inflammatory agent, or else to warn the patient and emphasise the importance of self-monitoring. Where necessary, adjust the dose during and after treatment with the anti-inflammatory agent.

• **Alcohol:** increases the hypoglycaemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycaemic coma.

Avoid alcohol or medicines containing alcohol.

Combinations requiring precautions for use

Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur when one of the following drugs is taken:

Other antidiabetic agents (insulins, acarbose, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H2-receptor antagonists, MAOIs, sulfonamides, clarithromycin and nonsteroidal anti-inflammatory agents.

The following products may cause an increase in blood glucose levels

Combination which is not recommended

• **Danazol**: diabetogenic effect of danazol.

If the use of this active substance cannot be avoided, warn the patient and emphasise the importance of urine and blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic agent during and after treatment with danazol.

Combinations requiring precautions during use

• **Chlorpromazine** (neuroleptic agent): high doses (>100 mg per day of chlorpromazine) increase blood glucose levels (reduced insulin release).

Warn the patient and emphasise the importance of blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with the neuroleptic agent.

• **Glucocorticoids** (systemic and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin: increase in blood glucose levels with possible ketosis (reduced tolerance to carbohydrates due to glucocorticoids).

Warn the patient and emphasise the importance of blood glucose monitoring, particularly at the start of treatment. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with glucocorticoids.

• **Ritodrine, salbutamol, terbutaline**: (I.V.)

Increased blood glucose levels due to beta-2 agonist effects.

Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin.

Combination which must be taken into account

• **Anticoagulant therapy** (Warfarin ...):

Sulfonylureas may lead to potentiation of anticoagulation during concurrent treatment.

Adjustment of the anticoagulant may be necessary.

FERTILITY, PREGNANCY AND LACTATION

Metformin

Pregnancy

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus.

Breast-feeding

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breast-feeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breast-feeding and the potential risk to adverse effects on the child.

Fertility

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Gliclazide

Pregnancy:

There is no or limited amount of data (less than 300 pregnancy outcomes) from the use of gliclazide in pregnant women, even though there are few data with other sulfonylureas.
Studies in animals have shown reproductive toxicity.

As a precautionary measure, it is preferable to avoid the use of Gliclazide during pregnancy.
Control of diabetes should be obtained before the time of conception to reduce the risk of congenital abnormalities linked to uncontrolled diabetes.

Oral hypoglycaemic agents are not suitable, insulin is the drug of first choice for treatment of diabetes during pregnancy. It is recommended that oral hypoglycaemic therapy is changed to insulin before a pregnancy is attempted, or as soon as pregnancy is discovered.

Breast-feeding:

It is unknown whether gliclazide or its metabolites are excreted in human milk. Given the risk of neonatal hypoglycaemia, the product is therefore contra-indicated in breast-feeding mothers. A risk to the newborns/infants cannot be excluded.

Fertility
No effect on fertility or reproductive performance was noted in male and female rats

Effects on ability to drive and use machines
Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.
However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulfonylureas, insulin or meglitinides).

UNDESIRABLE EFFECTS
Metformin
During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to increase slowly the doses.
The following adverse reactions 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.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Metabolism and nutrition disorders
Very rare
• Lactic acidosis
• Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.
Nervous system disorders
Common
• Taste disturbance
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. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.
Hepatobiliary disorders
Very rare
• Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.
Skin and subcutaneous tissue disorders
Very rare
• Skin reactions such as erythema, pruritus, urticaria

Paediatric population
In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

Gliclazide
Based on the experience with gliclazide, the following undesirable effects have been reported.
The most frequent adverse reaction with gliclazide is hypoglycaemia

As for other sulfonylureas, treatment with Diamicron 80 mg Tablets can cause hypoglycaemia, if mealtimes are irregular and, in particular, if meals are skipped. Possible symptoms of hypoglycaemia are: headache, intense hunger, nausea, vomiting, lassitude, sleep disorders, agitation, aggression, poor concentration, reduced awareness and slowed reactions, depression, confusion, visual and speech disorders, aphasia, tremor, paresis, sensory disorders, dizziness, feeling of powerlessness, loss of self-control, delirium, convulsions, shallow respiration, bradycardia, drowsiness and loss of consciousness, possibly resulting in coma and lethal outcome.

In addition, signs of adrenergic counter-regulation may be observed: sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmia.
Usually, symptoms disappear after intake of carbohydrates (sugar). However, artificial sweeteners have no effect. Experience with other sulfonylureas shows that hypoglycaemia can recur even when measures prove effective initially.

If a hypoglycaemic episode is severe or prolonged, and even if it is temporarily controlled by intake of sugar, immediate medical treatment or even hospitalisation are required.

Gastrointestinal disturbances, including abdominal pain, nausea, vomiting dyspepsia, diarrhoea, and constipation have been reported: if these should occur they can be avoided or minimised if gliclazide is taken with breakfast.

The following undesirable effects have been more rarely reported:
• Skin and subcutaneous tissue disorders: rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes, bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis), and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS).
• Blood and lymphatic system disorders: changes in haematology are rare. They may include anaemia, leucopenia, thrombocytopenia, granulocytopenia. These are in general reversible upon discontinuation of medication.
• Hepato-biliary disorders: raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis (isolated reports). Discontinue treatment if cholestatic jaundice appears. These symptoms usually disappear after discontinuation of treatment.
• Eye disorders:
Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.
• Class attribution effects:
As for other sulfonylureas, the following adverse events have been observed: cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia, allergic vasculitis, hyponatremia, elevated liver enzyme levels and even impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulfonylurea or led to life-threatening liver failure in isolated cases.

OVERDOSE

Metformin

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

Gliclazide

An overdose of sulfonylureas may cause hypoglycaemia.
Moderate symptoms of hypoglycaemia, without any loss of consciousness or neurological signs, must be corrected by carbohydrate intake, dose adjustment and/or change of diet. Strict monitoring should be continued until the doctor is sure that the patient is out of danger.

Severe hypoglycaemic reactions, with coma, convulsions or other neurological disorders are possible and must be treated as a medical emergency, requiring immediate hospitalisation.

If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid I.V. injection of 50 mL of concentrated glucose solution (20 to 30 %). This should be followed by continuous infusion of a more dilute glucose solution (10 %) at a rate that will maintain blood glucose levels above 1 g/L. Patients should be monitored closely and, depending on the patient's condition after this time, the doctor will decide if further monitoring is necessary.

Dialysis is of no benefit to patients due to the strong binding of gliclazide to proteins.

PHARMACODYNAMIC PROPERTIES

Metformin

Pharmacotherapeutic group: Blood glucose lowering drugs. Biguanides; ATC code: A10BA02
Mechanism of action
Metformin 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 3 mechanisms:
• Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
• In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
• And 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 (GLUTs) known to date.
Pharmacodynamic effects
In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.
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 or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy

The prospective randomised study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with 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).

Benefit regarding clinical outcome has not been shown for metformin used as second-line therapy, in combination with a sulfonylurea.

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.

Paediatric population

Controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year demonstrated a similar response in glycaemic control to that seen in adults.

Pharmacokinetic properties

Absorption

After an oral dose of metformin hydrochloride tablet, maximum plasma concentration (C_{max}) is reached in approximately 2.5 hours (t_{max}). Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

At the recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following oral administration of a 850 mg tablet, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these findings is unknown.

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 (Vd) ranged between 63-276 l.

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

Elimination
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 6.5 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.

Characteristics in specific groups of patients
Renal impairment
The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations.

Paediatric population
Single dose study: After single doses of metformin hydrochloride 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC0-t) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

Gliclazide
Pharmacotherapeutic group: sulfonamides, urea derivatives. ATC code: A10BB09

Mechanism of action
Gliclazide is a hypoglycaemic sulfonylurea antidiabetic active substance differing from other related compounds by an N-containing heterocyclic ring with an endocyclic bond.

Gliclazide reduces blood glucose levels by stimulating insulin secretion from the β-cells of the islets of Langerhans. Increase in postprandial insulin and C-peptide secretion persists after two years of treatment.

In addition to these metabolic properties, gliclazide has haemovascular properties.

Clinical efficacy and safety
Effects on insulin release:
In type 2 diabetics, gliclazide restores the first peak of insulin secretion in response to glucose and increases the second phase of insulin secretion. A significant increase in insulin response is seen in response to stimulation induced by a meal or glucose.

Haemovascular properties:
Gliclazide decreases microthrombosis by two mechanisms which may be involved in complications of diabetes:
• A partial inhibition of platelet aggregation and adhesion, with a decrease in the markers of platelet activation (beta thromboglobulin, thromboxane B_2),
• An action on the vascular endothelium fibrinolytic activity with an increase in TPA activity.

Pharmacokinetic properties
Absorption
Plasma levels increase reaching maximal concentrations between 2 and 6 hours.
Gliclazide is well absorbed. Food intake does not affect the rate or degree of absorption.

Distribution
Plasma protein binding is approximately 95%. The volume of distribution is around 19 litres.

Biotransformation
Gliclazide is mainly metabolised in the liver and excreted in the urine; less than 1% of the dose is excreted unchanged in the urine. No active metabolites have been detected in plasma.

Elimination
The elimination half-life of gliclazide is between 10 and 12 hours.

Linearity/non-linearity
The relationship between the dose administered between 40 and 400mg and the mean plasma concentrations is linear.

Special populations
Elderly
No clinically significant changes in pharmacokinetic parameters have been observed in elderly patients.

PRECLINICAL SAFETY DATA
Metformin
Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

Gliclazide

Preclinical data reveal no special hazards for humans based on conventional studies of repeated dose toxicity and genotoxicity. Long term carcinogenicity studies have not been done. No teratogenic changes have been shown in animal studies, but lower foetal body weight was observed in animals receiving doses 9.4 fold higher than the maximum recommended dose in humans. Fertility and reproductive performance were unaffected after gliclazide administration in animal studies.

EXPIRY DATE:
Do not use later than the date of expiry.

STORAGE:
Store at a temperature not exceeding 30^{o}C. Protected from light and moisture. Keep out of reach of children.

PRESENTATION AND AVAILABILITY:
AZUKON-M is available in blister pack of 10 tablets.

MARKETED BY

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IN/AZUKON M 80,500mg/JAN-2016/01/PI