1. **NAME OF THE MEDICINAL PRODUCT**

   Metformin 500mg Tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

   One film-coated tablet contains metformin hydrochloride 500mg.

   For excipients see 6.1

3. **PHARMACEUTICAL FORM**

   Film-coated tablets

   White coloured, film-coated, round, biconvex tablets.

4. **CLINICAL PARTICULARS**

4.1. **Therapeutic indications**

   - Non-insulin-dependent diabetes (NIDDM, type II) and, in particular, in obese patients, when adequate dietary treatment has failed.

   - Metformin 500mg tablets can be given alone as initial therapy, or can be administered in combination with sulphonylureas after careful assessment of the contraindications.

4.2. **Posology and method of administration**

   **Dosage**

   **Usual dosage:**

   The required daily dose ranges from 0.5 to 3g. The usual starting dose is one 500mg tablet three times a day or one 850mg tablet twice a day. The daily dose should be divided and taken with or after meals in order to minimise the gastro-intestinal side effects. If diabetic control is incomplete a cautious increase in dosage to a maximum of 3g daily is justified. No additional benefit can usually be achieved by use of doses exceeding 3g daily. Once control has been achieved it may be possible to reduce the daily dose.

   **In cases of metabolic decompensation:**

   The metformin hydrochloride dosage may be reduced in cases of metabolic decompensation. If only small daily doses are administered an omission of one metformin hydrochloride dose should be tried. This is of importance in elderly patients to reduce the risk of lactic acidosis.

   **Children and juveniles:**
Metformin 500mg Tablets are not recommended for use in children.

**Elderly patients:**

Metformin 500mg Tablets are indicated for use in the elderly.

**Further dosage information**

**Combination with sulphonylureas:**

Metformin 500mg Tablets may be used in combination with sulphonylureas if monotherapy with metformin hydrochloride does not lead to a satisfactory response. However, it should be noted that metformin hydrochloride and sulphonylureas have a different mode of action and therefore an additive or potentiating effect of these drugs might cause a hypoglycaemic shock.

**Substitution for sulphonylureas:**

Metformin 500mg Tablets may be used instead of sulphonylureas in patients who formerly have been treated with sulphonylureas.

**Method of administration**

Metformin 500mg Tablets should be taken whole with a glass of water during or after meals. They should not be chewed.

**Monitoring advice**

See special warnings and precautions for use.

### 4.3. Contraindications

- In patients with non-insulin-dependent diabetes (NIDDM, type II), if sulphonylurea therapy has completely failed
- Diabetic precoma, coma and ketoacidosis
- Hypersensitivity to metformin hydrochloride
- Impaired renal function of any degree
- Chronic liver disease
- Severe cardiovascular impairment.
- Cardiac failure and recent myocardial infarction.
- Severe peripheral vascular disease
- Acute severe disorders, for example infections with fever, pancreatitis or trauma
- Dehydration
- History of or conditions associated with lactic acidosis such as shock or pulmonary insufficiency, alcoholism (acute or chronic), and conditions associated with hypoxaemia
- Reduced diet (< 1000 kcal or 4200 kJ per day)
- Pregnancy.
4.4. Special warnings and precautions for use

Warnings

- In patients with impaired liver function, lactate clearance may be restricted.
- The risks of lactic acidosis and accumulation are determined by renal function. Therefore, metformin hydrochloride therapy requires a normal renal function, which should be monitored continuously, particularly in the elderly.
- In elderly patients (approximately over the age of 65 years) metabolism is reduced and therefore a risk/benefit assessment should be carried out.
- During concomitant therapy with sulphonylureas or insulin, blood glucose levels should be monitored because combined therapy may cause hypoglycaemia. Stabilisation of diabetic patients with metformin hydrochloride and insulin should be carried out in a hospital until the correct ratio of the two drugs has been obtained.
- Metformin hydrochloride therapy should be stopped before, during and after surgery under general anaesthesia.
- Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such studies are planned, metformin hydrochloride should be discontinued at the time of, or prior to, the procedure and withheld for 48 hours subsequent to the procedure and re-instituted only after renal function has been re-evaluated and found to be normal.
- Patients receiving continuous metformin hydrochloride therapy should have an annual estimation of Vitamin B₁₂ levels because of reports of decreased Vitamin B₁₂ absorption.

Precautions for use

- Patients should be warned to consult a physician immediately if they suddenly suffer from muscle spasms, dyspepsia, abdominal pain and fatigue, since these symptoms may indicate lactic acidosis. Lactic acidosis is accompanied by acidic dyspnoea, abdominal pain, hyperthermia, comatose state, decrease of blood pH value and increase of lactate value.
- Serum creatinine levels should be determined before and four weeks after metformin hydrochloride therapy has been started. Regular measurements should take place once or twice a year unless required earlier due to intercurrent disorders. In elderly patients serum creatinine values often are not meaningful. Therefore, creatinine clearance should be tested before the onset of metformin hydrochloride therapy.

4.5. Interactions with other medicinal products and other forms of interaction

Contraindicated

During treatment with Metformin 500mg Tablets alcohol should be strictly avoided. Alcohol may enhance the hypoglycaemic effect and produce an increased risk of lactic acidosis.

Precaution for use

An increase of the antihyperglycaemic effect of metformin hydrochloride is possible in the event of concomitant administration with medicinal products for the same indication, for example:
- Insulin
- Oral antidiabetic drugs, of the sulphonylurea and acarbose type

An increase of the antihyperglycaemic effect of metformin hydrochloride is also possible in the event of concomitant administration with medicinal products for other indications which possess blood glucose-lowering effects of their own, for example:

- NSAIDs, e.g. salicylates or pyrazolones
- MAO inhibitors
- Oxytetracycline
- ACE inhibitors
- Clofibrate derivatives
- Cyclophosphamide and its derivatives

⇒ The combination of metformin and the above mentioned drugs can induce hypoglycaemia.

Moreover, during permanent therapy, beta-blockers and antisympathotonic drugs, such as clonidine, reserpine or guanethidine, may decrease blood glucose levels. However, of particular clinical relevance is their reducing action on the hormonal and neural counterregulation during hyperglycaemia, which in turn also impairs the subjective perception of hypoglycaemic warning signs.

A decrease of the antihyperglycaemic effect of metformin hydrochloride in combination with one of the following drugs may occur:

- Glucocorticoids
- Oestrogen-Progestogen-Combinations
- Adrenaline and other Sympathomimetics
- Glucagon
- Thyroid hormones
- Thiazides and loop diuretics
- Diazoxide
- Phenothiazines
- Nicotinic acid derivatives

Guar: A decrease of the absorption of metformin hydrochloride may lead to an attenuation of metformin effects.

Cimetidine: Substances which delay the elimination of metformin hydrochloride, e.g. cimetidine, may increase the risk of lactic acidosis.

Phenprocoumone: Elimination of phenprocoumone and other coumarins may be accelerated during metformin hydrochloride therapy. Therefore the blood coagulation inhibiting effect may be decreased and frequent controls of blood coagulation are necessary.

To be taken into account

During maintenance therapy the onset or termination of any other additional therapy can disturb the control of diabetes.
4.6. Pregnancy and lactation

Pregnancy

During pregnancy the administration of Metformin 500mg Tablets is contra-indicated. Diabetes mellitus should be treated with insulin during pregnancy or when pregnancy is desired. Animal studies have shown no particular effects with respect to reproduction and fertility. In man insufficient experience with metformin hydrochloride during pregnancy has been obtained.

Use during lactation

The use of Metformin 500mg Tablets should be avoided in women who are breast-feeding. No information is available on whether metformin hydrochloride or its metabolites are excreted in the breast milk.

4.7. Effects on ability to drive and use machines

When used as monotherapy metformin hydrochloride does not influence the ability to drive or operate machinery. In cases of combined therapy with sulphonylureas or other drugs with blood glucose lowering effects, hypoglycaemia may occur and, hence, such combinations may produce minor or moderate adverse effects. Patients undergoing such combination therapy should be warned about the possible adverse effects of hypoglycaemia.

4.8. Undesirable effects

Frequently arising undesirable effects are: Gastro-intestinal disturbances

Metformin 500mg Tablets are normally well tolerated, but at the beginning of metformin hydrochloride therapy gastro-intestinal disturbances, such as nausea, vomiting, abdominal pain, diarrhoea, anorexia and metallic taste occur in 5 - 20% of patients. These gastro-intestinal disturbances are generally of minor importance and require no termination of metformin hydrochloride therapy. The frequency and severity of these gastro-intestinal disturbances can be reduced markedly by starting with low and gradually increasing metformin hydrochloride doses and by administration of metformin hydrochloride with or after meals. About 5% of all patients do not tolerate metformin hydrochloride therapy.

Very rarely arising undesirable effects are: Hypersensitivity and lactic acidosis

- Hypersensitivity reactions of the skin.
- Lactic acidosis.

Under metformin hydrochloride therapy lactic acidosis with coma and death is possible. Lactic acidosis induced by metformin hydrochloride is an indicator for a general cell toxicity and is accompanied by impaired hepatic lactate clearance and increased muscular lactate release. Although metformin hydrochloride-induced lactic acidosis occurs very rarely the lethality reaches 50%.
Causes of lactic acidosis: Apart from overdosage other causes of lactic acidosis may be renal insufficiency, impaired liver function, alcohol consumption, other diseases with effects on oxidative metabolism, for example cardiac decompensation or severe infections and catabolic conditions as well as interactions with other drugs.

Symptoms of lactic acidosis: At first lactic acidosis resembles the gastro-intestinal side-effects of metformin hydrochloride, for example nausea, vomiting, diarrhoea and abdominal pain. However, within a few hours the complete clinical picture of lactic acidosis with muscle pains, hyperventilation, clouding of consciousness and coma may develop. On suspicion of lactic acidosis metformin therapy must be immediately stopped and the patient must be treated at once as an emergency in hospital.

Reported single cases:

Inhibition of the absorption of Vitamin B₁₂ or folic acid may cause megaloblastic anaemia. Therefore, patients receiving continuous metformin hydrochloride therapy should have an annual estimation of Vitamin B₁₂ levels and, if necessary, Vitamin B₁₂ has to be given parenterally. Persisting gastro-intestinal disturbances require the termination of metformin hydrochloride therapy.

4.9. Overdose

Human experience

Intoxication with metformin hydrochloride does not lead to hypoglycaemia but lactic acidosis may develop. Hypoglycaemia can occur when metformin hydrochloride is given concomitantly with sulphonylureas, alcohol or insulin.

Management of overdosage in man

In cases of metformin hydrochloride overdosage, for example in attempted suicide, or if signs of lactic acidosis are shown, patients must be admitted to a hospital as an emergency. The diagnosis of lactic acidosis should be confirmed by determination of lactate and metformin hydrochloride concentrations. Haemodialysis is the most effective measure to eliminate lactate and metformin hydrochloride. Symptomatic treatment includes circulatory stabilisation, compensation of acidosis and elimination of hypoxia. The metformin hydrochloride concentration in erythrocytes is a good indicator for accumulation and can be used to decide whether repeated haemodialysis is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Metformin hydrochloride is a biguanide oral antihyperglycaemic agent (ATC Code A10BA02) and reduces elevated blood glucose levels only in patients with non-insulin-dependent diabetes (NIDDM), but does not increase insulin secretion and does not cause hypoglycaemia or increased weight gain. Its mode of action is multifactorial and not yet
completely understood. However, the augmentation of glucose uptake into peripheral tissues may influence glucose utilisation. Furthermore, the effects of metformin hydrochloride include reduced hepatic gluconeogenesis and delayed intestinal glucose absorption which may explain the blood glucose-lowering effect. The efficacy of metformin hydrochloride is dependent on a minimum concentration of insulin. A slight influence of the insulin secretion by metformin hydrochloride is possible but a clinical relevance is not very likely. Metformin hydrochloride seems to potentiate insulin action by enhancing insulin binding to its receptors and by facilitating steps in the post-receptor pathways of insulin-action. Apart from the glucose-lowering effect, metformin hydrochloride reduces the serum triglyceride level and possesses antithrombotic properties.

5.2. Pharmacokinetic properties

After oral administration metformin hydrochloride is incompletely absorbed from the gastro-intestinal tract. The oral bioavailability of usual doses is 50 - 60%. The maximum plasma concentration is achieved after about 2 hours. Gastrointestinal absorption is complete within 6 hours of ingestion. The volume of distribution lies between 63 and 276 litres. Metformin hydrochloride is rapidly distributed but a slow transfer to a deep compartment seems to occur. Metformin hydrochloride does not bind to plasma proteins but accumulates in the salivary glands, duodenum, kidneys and liver. No metabolites or conjugates of metformin hydrochloride have been identified. Metformin hydrochloride is completely eliminated by renal excretion and the mean plasma elimination half-life ranges between 1.5 and 4.5 hours. A quantitatively minor terminal elimination phase, probably out of the deep compartment, with a longer mean half-life ranging from 8.9 to 19 hours, has been observed. The renal clearance of metformin hydrochloride ranges between 350 and 550ml/min and correlates with the creatinine clearance, indicating that metformin hydrochloride is excreted by active tubular secretion. In patients with impaired renal function accumulation of metformin hydrochloride is probable.

5.3. Preclinical safety data

Acute toxicity:

Acute toxicity after different routes of administration and in different animals was investigated. The data indicate the highest toxicity of metformin hydrochloride after subcutaneous administration to guinea pigs and rabbits (LD_{50} = 150mg/kg) and intravenous administration to mice (LD_{50} = 180mg/kg). The toxicity after oral ingestion of metformin hydrochloride seems to be several times lower, rabbits and guinea pigs (LD_{50} 350 and 500mg/kg, respectively) being more sensitive than mice or rats (LD_{50} 1450mg/kg and 1000mg, respectively). Hence, in various animal species studied, after different routes of administration the LD_{50} values are considerably higher than the therapeutic dose range in humans (maximum approximately 40mg/kg/day). The data indicate a low potential of acute toxicity.

Chronic toxicity:

Studies with repeated administration of metformin hydrochloride to rats (up to 18 months), dogs (up to 18 months) and monkeys (up to 2 years) revealed no specific toxic effects.

Mutagenic and carcinogenic effects:
Bacterial tests for mutagenicity of metformin hydrochloride were negative but chromosomal alterations were observed in vitro in mammalian cells. The relevance of these effects remains obscure. Long-term animal studies failed to detect any oncogenic properties of metformin hydrochloride.

Reproductive toxicity:

No teratogenic properties of metformin hydrochloride have been found in rats. The no adverse-effect level (NOAEL) of metformin hydrochloride in rats was estimated to be 300mg/kg/day for embryotoxicity and female reproduction and up to 600mg/kg/day for male fertility. No teratogenic effects were observed in rabbits with doses up to 140mg/kg/day (p.o.). In rats doses up to 600mg/kg/day administered p.o. pre- and postnatally showed no effects.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core
- Sodium starch glycollate
- Maize starch
- Povidone
- Colloidal anhydrous silica
- Magnesium stearate

Film-coating
- Hypromellose
- Titanium dioxide E 171
- Propylene glycol
- Macrogol 6000
- Purified talc

6.2. Incompatibilities

None applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Do not store above 25°C.

6.5. Nature and contents of container
PVC/PVDC/Aluminium blister packs in outer cardboard cartons.
Contents: 84 film-coated tablets.

6.6. Instructions for use and handling

No special precautions are required.

7. MARKETING AUTHORISATION HOLDER

8PM Chemist Limited
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West Midlands
WV13 2NF
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 18599/0001

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