SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metformin Hydrochloride 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metformin Hydrochloride 500 mg film-coated tablets

Each film-coated tablet contains 500 mg of Metformin Hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

White round biconvex film-coated tablets with “500” debossed on one side & plain on other.

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 can be given alone as initial therapy, or can be administered in combination with sulphonylureas after careful assessment of the contra-indications.

• In adults, Metformin may be used as monotherapy or in combination with other oral antidiabetic agents or with insulin.

• In children from 10 years of age and adolescents, Metformin may be used as monotherapy or in combination with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin as first-line therapy after diet failure (see section 5.1).

4.2 Posology and method of administration

Posology

Adults with normal renal function (GFR ≥90 mL/min)

Monotherapy and combination with other oral antidiabetic agents
Initially, 500 mg every 8 hours or 850 mg every 12 hours, with or after food. Diabetic control may be achieved within a few days but the full effect can be delayed for up to 2 weeks. If control is incomplete, the dosage may be increased with care up to a maximum of 3 g daily taken as 3 divided doses 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. Once adequate control has been achieved a reduction in dosage may be possible.
If transfer from another oral antidiabetic agent is intended, discontinue the other agent and initiate metformin at the dose indicated above.

Combination with insulin
Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin hydrochloride is given at the usual starting dose of 500 mg or 850 mg 2 or 3 times daily, while insulin dosage is adjusted based on blood glucose measurements.

Elderly
Metformin should be used with caution in elderly patients whose renal function may be reduced. Regular assessment of renal function is necessary (see section 4.4).
In cases of metabolic decompensation:
The metformin dosage may be reduced in cases of metabolic decompensation. If only small daily doses are administered an omission of one metformin dose should be tried. This is of importance in elderly patients to reduce the risk of lactic acidosis.

Patients with renal impairment
A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

GFR mL/min	Total maximum daily dose (to be divided into 2-3 daily doses)	Additional considerations
60-89	3000 mg	Dose reduction may be considered in relation to declining renal function.
45-59	2000 mg	Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin. The starting dose is at
30-44	1000 mg	

		most half of the maximum dose.
<30	-	Metformin is contraindicated.

Paediatric population
Monotherapy and combination with insulin
• Metformin can be used in children from 10 years of age and adolescents.
• The usual starting dose is 500 mg or 850 mg metformin hydrochloride once daily, given during 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 hydrochloride is 2 g daily, taken as 2 or 3 divided doses.
Further dosage information
Combination with sulphonylureas:
Metformin hydrochloride may be used in combination with sulphonylureas if monotherapy with metformin does not lead to a satisfactory response. However, it should be noted that metformin 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 hydrochloride may be used instead of sulphonylureas in patients who formerly have been treated with sulphonylureas.

Method of administration
For oral administration.

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 pre-coma, coma and ketoacidosis
- Hypersensitivity to metformin or any of the excipients listed in section 6.1
- Severe renal failure (GFR <30 ml/min)
- Chronic liver disease or hepatic insufficiency
- Severe cardiovascular impairment

- Acute or chronic disease which may cause tissue hypoxia such as decompensated heart failure or respiratory failure, recent myocardial infarction, shock
- Severe peripheral vascular disease
- Acute conditions with the potential to alter renal function, for example infections with fever, pancreatitis or trauma
- Dehydration, severe infection, shock
- History of or conditions associated with lactic acidosis such as shock or pulmonary insufficiency, alcoholism (acute or chronic), acute alcohol intoxication
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Reduced diet (< 1000kcal or 4,200kJ per day)

4.4 Special warnings and precautions for use

Lactic acidosis:

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin tablets should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformintreated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).
Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (> 5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.
Patients with known or suspected mitochondrial diseases:

In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS)

syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Surgery:

Metformin must be discontinued at the time of surgery under general, spinal or
epidural anesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been reevaluated and found to be stable.

Renal function:

GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR <30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section 4.3.

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 (see section 4.3).

Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.5.

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

Metformin alone does not cause hypoglycaemia.
During concomitant therapy with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides), blood glucose levels should be monitored because combined therapy may cause hypoglycaemia.

Stabilisation of diabetic patients with metformin and insulin should be carried out in a hospital until the correct ratio of the two drugs has been obtained.
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 may reduce vitamin B_{12} serum levels. The risk of low vitamin B_{12} levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B_{12} deficiency. In case of suspicion of vitamin B_{12} deficiency (such as anaemia or neuropathy), vitamin B_{12} serum levels should be monitored. Periodic vitamin B_{12} monitoring could be necessary in patients with risk factors for vitamin B_{12} deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B_{12} deficiency provided in line with current clinical guidelines.

Serum creatinine levels should be determined before and four weeks after metformin 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 therapy.
Excipients warning:
This medicine contains less than 1 mmol sodium (23 mg) per tablets, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment. *Iodinated contrast agents*

Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.4.

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

An increase of the anti-hyperglycaemic effect of metformin 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 anti-hyperglycaemic effect of metformin 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 anti-sympathotonic 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 counter regulation during hyperglycaemia, which in turn also impairs the subjective perception of hypoglycaemic warning signs.

A decrease of the anti-hyperglycaemic effect of metformin in combination with one of the following drugs may occur:

- Glucocorticoids (systemic or local route)
- Oestrogen-Progestagen-Combinations
- Adrenaline and other Sympathomimetics
- Glucagon
- Thyroid hormones
- Thiazides and loop diuretics. Diuretics especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function.
- Diazoxide
- Phenothiazines
- Nicotinic acid derivatives

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 the therapy with the respective medicinal products and upon its discontinuation.

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

Beta2 agonists such as salbutamol or terbutaline (used to treat asthma)

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

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

Iodinated contrast agents:

Intravascular administration of iodinated contrast agent may lead to renal failure resulting in Metformin accumulation and an increased risk of lactic acidosis.

Metformin must be discontinued prior to or at the time of the test and not be reinstituted until 48 Hours afterwards and only after renal function has been re- evaluated and found to be normal.

During maintenance therapy, the onset or termination of any other additional therapy can disturb the control of diabetes.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Uncontrolled hyperglycaemia in the periconceptional phase and during pregnancy is associated with increased risk of congenital abnormalities, pregnancy loss, pregnancy-induced hypertension, preeclampsia, and perinatal mortality. It is important to maintain blood glucose levels as close to normal as possible throughout pregnancy, to reduce the risk of adverse hyperglycaemia-related outcomes to the mother and her child.

Metformin crosses the placenta with levels that can be as high as maternal concentrations.

A large amount of data on pregnant women (more than 1000 exposed outcomes) from a register-based cohort study and published data (meta-analyses, clinical studies, and registries) indicates no increased risk of congenital abnormalities nor feto/neonatal toxicity after exposure to metformin in the periconceptional phase and/or during pregnancy.

There is limited and inconclusive evidence on the metformin effect on the long-term weight outcome of children exposed in utero. Metformin does not appear to affect motor and social development up to 4 years of age in children exposed during pregnancy although data on long term outcomes are limited.

If clinically needed, the use of metformin can be considered during pregnancy and in the periconceptional phase as an addition or an alternative to insulin.

4.7 Effects on ability to drive and use machines

When used as monotherapy metformin does not cause hypoglycaemia and influence the ability to drive or operate machinery. In cases of combined therapy with sulphonylureas or other drugs (insulin or meglitinides) 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

Metabolism & Nutrition Disorders:

The following convention has been utilised for the classification of frequency:

Very common, ≥ 1/10; common, ≥1/100 and < 1/10; uncommon, ≥1/1000 and < 1/100; rare, ≥ 1/10000 and < 1/1000; very rare, < 1/10000; not known (cannot be estimated from the available data)

There are no modern clinical studies available that can be used to determine the frequency of undesirable effects.

Gastrointestinal disturbances occur in 5-20% of patients at the beginning of metformin therapy. These effects are generally of minor importance and do not

require termination of metformin therapy. The frequency and severity can be reduced markedly by starting with a low dose and gradually increasing the dose and by administration of metformin with or after meals.
About 5% of all patients do not tolerate metformin therapy. Persisting gastrointestinal disturbances require the termination of metformin therapy.

Nervous System Disorders:

Common: Taste disturbance

Immune System Disorders:

Very rare: Hypersensitivity (including hypersensitivity reactions of the skin).

Common:
- Vitamin B_{12} decrease/deficiency (see section 4.4).

Very rare:
Lactic acidosis (symptoms include gastrointestinal disorders, muscle pains, muscle spasms, fatigue, dyspnoea, hyperthermia, hyperventilation, decrease of blood pH, increase of lactate value, clouding of consciousness and coma).
On suspicion of lactic acidosis, metformin therapy must be immediately stopped and the patient must be treated at once as an emergency in hospital.

Gastro-intestinal disorders:

Very common: nausea, vomiting, abdominal pain, diarrhoea, anorexia and metallic taste 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: liver function test abnormal; hepatitis resolving upon discontinuation of Metformin.

Skin & Subcutaneous Tissue Disorders:

Very rare: erythema, pruritus, urticaria.

Paediatric population:

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected

adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Human experience

Intoxication with metformin does not lead to hypoglycaemia even at doses of up to 85 g but lactic acidosis may develop in such circumstances. Hypoglycaemia can occur when metformin is given concomitantly with sulphonylureas, alcohol or insulin.

Management of over dose

In cases of metformin over dosage, 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 concentrations. Haemodialysis is the most effective measure to eliminate lactate and metformin. Symptomatic treatment includes circulatory stabilisation, compensation of acidosis and elimination of hypoxia. The metformin 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 is a biguanide oral anti-hyperglycaemic agent (ATC Code A10B A02) 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 include reduced hepatic gluconeogenesis and delayed intestinal glucose absorption which may explain the blood glucose-lowering effect. The efficacy of metformin is dependent on a minimum concentration of insulin. A slight influence of the insulin secretion by metformin is possible but a clinical relevance is not very likely. Metformin 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 reduces the serum triglyceride level and possesses antithrombotic properties.

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 for 1 year demonstrated a similar response in glycaemic control to that seen in adults.

5.2 Pharmacokinetic properties

Absorption

After oral administration metformin is incompletely absorbed from the gastrointestinal 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 is rapidly distributed but a slow transfer to a deep compartment seems to occur. Metformin does not bind to plasma proteins but accumulates in the salivary glands, duodenum, kidneys and liver. No metabolites or conjugates of metformin have been identified. Metformin 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 ranges between 350 and 550 ml/min and correlates with the creatinine clearance, indicating that metformin is excreted by active tubular secretion. In patients with impaired renal function accumulation of metformin is probable.

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 (see section 4.2).

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 (Cmax) 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**.**

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} = 150 mg/kg) and intravenous administration to mice (LD_{50} = 180 mg/kg). The toxicity after oral ingestion of metformin hydrochloride seems to be several times lower, rabbits and guinea pigs (LD_{50} 350 and 500 mg/kg, respectively) being more sensitive than mice or rats (LD_{50} 1450 mg/kg and 1000 mg, 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 40 mg/kg/day). The data indicate a low potential of acute toxicity.

Chronic toxicity:

Studies with repeated administration of metformin 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 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.

Reproductive toxicity:

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

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

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

Not 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

Blister pack of PVC/PVDC/Al or PVC/Al

Each pack contains 28, 56, 60 or 84 film-coated tablets (not all pack sizes may be marketed).

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Lyrus Life Sciences Limited
C/O Thakur- Chabert Suite 410, 4th floor
1 Harefield Road
Uxbridge
England
UB8 1EX

8 MARKETING AUTHORISATION NUMBER(S)

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