Summary of product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

ILET B1 (Glimepiride 1 mg and Metformin Hydrochloride 500 mg Extended release tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated bilayered tablet contains 1 mg Glimepiride and 500 mg Metformin Hydrochloride

Excipient(s) with known effects:

Each tablet contains 224.25 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Bilayered uncoated tablet.

Caplet shaped bi layered smooth surface, one layer with white color and one layer with yellow color uncoated tablets.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications

Glimepiride: Glimepiride is indicated for the treatment of type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate.

Metformin Hydrochloride:

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 prolonged-release tablets may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

For study results with respect to effects on glycaemic control and diabetic complications, (see section 5.1).

4.2 Posology and method of administration

Glimepiride:

For oral administration.

The basis for successful treatment of diabetes is a good diet, regular physical activity, as well as routine checks of blood and urine. Tablets or insulin cannot compensate if the patient does not

keep to the recommended diet.

Dose is determined by the results of blood and urinary glucose determinations.

The starting dose is 1 mg glimepiride per day. If good control is achieved this dose should be used for maintenance therapy.

For the different dosage regimens appropriate strengths are available.

If control is unsatisfactory, the dosage should be increased, based on the glycaemic control, in a stepwise manner with an interval of about 1 to 2 weeks between each step, to 2, 3, or 4 mg glimepiride per day.

A dose of more than 4 mg glimepiride per day gives better results only in exceptional cases. The maximum recommended dose is 6 mg glimepiride per day.

In patients not adequately controlled with the maximum daily dose of metformin, concomitant glimepiride therapy can be initiated.

 While maintaining the metformin dose, the glimepiride therapy is started with a low dose, and is then titrated up depending on the desired level of metabolic control up to the maximum daily dose. The combination therapy should be initiated under close medical supervision.

In patients not adequately controlled with the maximum daily dose of glimepiride, concomitant insulin therapy can be initiated if necessary. While maintaining the glimepiride dose, insulin treatment is started at a low dose and titrated up depending on the desired level of metabolic control. The combination therapy should be initiated under close medical supervision.

Normally a single daily dose of glimepiride is sufficient. It is recommended that this dose be taken shortly before or during a substantial breakfast or - if none is taken - shortly before or during the first main meal.

If a dose is forgotten, this should not be corrected by increasing the next dose.

If a patient has a hypoglycaemic reaction on 1 mg glimepiride daily, this indicates that they can be controlled by diet alone.

In the course of treatment, as an improvement in control of diabetes is associated with higher insulin sensitivity, glimepiride requirements may fall. To avoid hypoglycaemia timely dose reduction or cessation of therapy must therefore be considered. Change in dose may also be necessary if there are changes in weight or life style of the patient, or other factors that increase the risk of hypo- or hyperglycaemia.

Switch over from other oral hypoglycaemic agents to glimepiride

A switch over from other oral hypoglycaemic agents to glimepiride can generally be done. For the

switch over to glimepiride the strength and the half-life of the previous medicinal product has to be taken into account. In some cases, especially in antidiabetics with a long half-life (e.g. chlorpropamide), a wash out period of a few days is advisable in order to minimise the risk of hypoglycaemic reactions due to the additive effect.

The recommended starting dose is 1 mg glimepiride per day. Based on the response the glimepiride dosage may be increased stepwise, as indicated earlier.

Switch over from insulin to glimepiride

In exceptional cases, where type 2 diabetic patients are regulated on insulin, a changeover to glimepiride may be indicated. The changeover should be undertaken under close medical supervision.

Special Populations

Patients with renal or hepatic impairment

See section 4.3.

Paediatric population

There are no data available on the use of glimepiride in patients under 8 years of age. For children aged 8 to 17 years, there are limited data on glimepiride as monotherapy (see sections 5.1 and 5.2).

The available data on safety and efficacy are insufficient in the paediatric population and therefore such use is not recommended.

Method of administration

Tablets should be swallowed without chewing with some liquid.

Metformin Hydrochloride:

Posology

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

Monotherapy and combination with other oral antidiabetic agents

The usual starting dose is one Metformin 500mg Prolonged-release Tablet once daily, taken with the evening meal.
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. The maximum recommended dose is 4 tablets of Metformin hydrochloride 500mg Prolonged- release Tablets daily with an evening meal.
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 glycaemic control is not achieved on 2000 mg once daily, 1000 mg twice daily should be considered, with both doses being given with food, at the time of the morning and evening meals. If glycaemic control is still not

achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

In patients already treated with metformin tablets, the starting dose of Metformin hydrochloride Prolonged-release Tablets should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin at a dose above 2000mg daily, switching to Metformin hydrochloride Prolonged-release Tablets is not recommended.

Metformin hydrochloride 750mg and 1000mg Prolonged-release Tablets are intended as maintenance therapy for patients currently treated with metformin tablets (prolonged or immediate release).

The dose of Metformin hydrochloride 750mg or 1000mg Prolonged-release Tablets should be equivalent to the daily dose of metformin tablets (prolonged or immediate release), up to a maximum dose of 1500mg or 2000mg respectively, given with the evening meal. After 10 to 15 days, it is recommended to check that the dose of Metformin hydrochloride 750mg or 1000mg Prolonged-release Tablets is adequate on the basis of blood glucose measurements.

In the event of transfer from another oral anti-diabetic agent: The other agent should be discontinued and titration should begin with Metformin hydrochloride 500mg Prolonged- release Tablets as indicated above, before switching to Metformin hydrochloride 750mg or Metformin hydrochloride 1000mg Prolonged –release Tablets.**.**

Combination with insulin

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of metformin is one 500 mg prolonged release tablet once daily taken in the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements. After titration, switching to Metformin 1000 mg Prolonged-release Tablet should be considered.

For patients already treated with metformin and insulin in combination therapy, the dose of Metformin hydrochloride 750mg or 1000mg Prolonged-release Tablets should be equivalent to the already used daily dose of metformin tablets up to a maximum of 1500mg or 2000mg respectively, given with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements.

Renal impairment

GFR should be assessed before initiation of treatment with Metformin hydrochloride Prolonged– release Tablets 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	Additional considerations
60-89	3000 mg	Dose reduction may be considered in relation to declining renal function. For patients with a GFR of 60- 89 ml/min, the maximum total daily dose is the currently approved dose for adults with normal 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 most half of the maximum dose.
30-44	1000 mg	
<30	-	Metformin is contraindicated.

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 (see section 4.4).

Paediatric population

In the absence of available data, Metformin hydrochloride Prolonged-release Tablets should not be used in children.

Method of administration

The tablets should not be chewed, split or crushed and should be taken whole with a glass of water.

4.3 Contraindications

For Glimepiride

Glimepiride is contraindicated in patients with the following conditions:
- hypersensitivity to glimepiride, other sulfonylureas or sulfonamides or to any of the excipients listed in section 6.1.
- diabetes mellitus type 1,
- diabetic coma
- ketoacidosis
- severe renal or hepatic function disorders. In case of severe renal or hepatic function disorders, a changeover to insulin is required.

For Metformin

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Diabetic pre-coma.
- Severe renal failure (GFR < 30 mL/min).
- 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.

4.4 Special warnings and precautions for use
For Glimepiride

Glimepiride must be taken shortly before or during a meal.

When meals are taken at irregular hours or skipped altogether, treatment with" Glimepiride Tablets" may lead to hypoglycaemia. Possible symptoms of hypoglycaemia include: headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, alertness and reaction time, depression, confusion, speech and visual disorders, aphasia, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia. In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmias.
The clinical picture of a severe hypoglycaemic attack may resemble that of a stroke.

Symptoms can almost always be promptly controlled by immediate intake carbohydrates (sugar). Artificial sweeteners have no effect.
It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycaemia may recur.

Severe hypoglycaemia or prolonged hypoglycaemia, only temporarily controlled by the usual amounts of sugar, require immediate medical treatment and occasionally hospitalisation. Factors favouring hypoglycaemia include:

- unwillingness or (more commonly in older patients) incapacity of the patient to cooperate

- undernutrition, irregular mealtimes or missed meals or periods of fasting

- alterations in diet

- imbalance between physical exertion and carbohydrate intake

- consumption of alcohol, especially in combination with skipped meals

- impaired renal function

- serious liver dysfunction

- overdosage with Glimepiride Tablets

- certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter regulation of hypoglycaemia (as for example in certain disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency).

- concurrent administration of certain other medicinal products (see section 4.5)

Treatment with glimepiride tablets requires regular monitoring of glucose levels in blood and urine. In addition, determination of the proportion of glycosylated haemoglobin is recommended. Regular hepatic and haematological monitoring (especially leucocytes and thrombocytes) are required during treatment with glimepiride.

In stress-situations (e.g. accidents, acute operations, infections with fever etc) a temporary switch to insulin may be indicated.

No experience has been gained concerning the use of glimepiride tablets in patients with severe impairment of liver function or dialysis patients. In patients with severe impairment of renal or liver function change over to insulin is indicated.

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anaemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a nonsulfonylurea alternative should be considered.

Glimepiride Tablets contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

For Metformin

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 should be temporarily discontinued and contact with a health care professional is recommended.

In patients treated with metformin, caution should be exercised when initiating therapy with medicinal products that may cause acute renal insufficiency (such as antihypertensives, diuretics and non-steroidal anti-inflammatory drugs (NSAIDs)). 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).

Diagnosis

Patients and/or their 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.

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.

Metformin is contraindicated in patients with acute and unstable heart failure (see section 4.3).

Administration of iodinated contrast agents

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 revaluated and found to be stable, see sections 4.2 and 4.5.

Surgery

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

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).

The tablet shells may be present in the faeces. It is recommended that patients be advised that this is normal

4.4   Interaction with other medicinal products and other forms of interaction

For Glimepiride

If glimepiride is taken simultaneously with certain other medicinal products, both undesired increases and decreases in the hypoglycaemic effect of glimepiride can occur. For this reason, other medicinal products should only be taken with the knowledge (or at the prescription) of the doctor.

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole).

Results from an in-vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2- fold by fluconazole, one of the most potent CYP2C9 inhibitors. Based on the experience with glimepiride and with other sulfonylureas, the following interactions have to be mentioned.

Potentiation of the blood-glucose-lowering effect and, thus in some instances hypoglycaemia may occur when one of the following medicinal products is taken, for example:

-    phenylbutazone, azapropazone and oxyfenbutazone,
-    insulin and oral antidiabetic products, such as metformin,
-    salicylates and p-amino-salicylic acid,
-    anabolic steroids and male sex hormones,
- chloramphenicol, certain long acting sulfonamides, tetracyclines, quinolone antibiotics clarithromycin,
-    coumarin anticoagulants,
-    fenfluramine,
-    disopyramide,

- fibrates,

- ACE inhibitors,

- fluoxetine, MAO-inhibitors,

- allopurinol, probenecid sulfinpyrazone,

- sympatholytics,

- cyclophosphamide, trophosphamide and iphosphamides,

- miconazole, fluconazole,

- pentoxifylline (high dose parenteral),

- tritoqualine

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following medicinal products is taken for example:

- oestrogens and progestogens

- saluretics, thiazide diuretics

- thyroid stimulating agents, glucocorticoids
- phenothiazine derivatives, chlorpromazine

- adrenaline and sympathicomimetics

- nicotinic acid (high dosages) and nicotinic acid derivatives

- laxatives (long term use)

- phenytoin, diazoxide

- glucagon, barbiturates and rifampicin

- acetazolamide

H2 antagonists, beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose-lowering effect.

Under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycaemic action of glimepiride in an unpredictable fashion.

Glimepiride may either potentiate or weaken the effects of coumarin derivatives.

Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction was observed when glimepiride was taken at least 4 hours before colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

For Metformin

<u>Concomitant use not recommended</u> 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.

<u>Combinations requiring precautions for use</u>

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.

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.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.Concomitant use with metformin:

- OCT1 inhibitors (such as verapamil) can decrease the effectiveness of metformin.
- OCT1 inducers (such as rifampicin) can increase the absorption of metformin from the gastrointestinal tract and its effectiveness.
- OCT2 inhibitors (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) can decrease the renal excretion of metformin and may result in increased plasma concentrations of metformin.
- OCT1 and OCT2 inhibitors (such as crisotinib and olaparib) can alter the efficacy and the 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.

4.5   Fertility, pregnancy and lactation

Pregnancy

For Glimepiride

Risk related to the diabetes

Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities and perinatal mortality. So the blood glucose level must be closely monitored during pregnancy in order to avoid the teratogenic risk. The use of insulin is required under such circumstances. Patients who consider pregnancy should inform their physician.

Risk related to glimepiride

There are no adequate data from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which likely was related to the pharmacologic action (hypoglycaemia) of glimepiride (see section 5.3).

Consequently, glimepiride should not be used during the whole pregnancy.

In case of treatment by glimepiride, if the patient plans to become pregnant or if a pregnancy is discovered, the treatment should be switched as soon as possible to insulin therapy.

Breast-feeding

The excretion in human milk is unknown. Glimepiride is excreted in rat milk. As other sulfonylureas are excreted in human milk and because there is a risk of hypoglycaemia in nursing infants, breast-feeding is advised against during treatment with glimepiride.

Fertility

No data on fertility is available

For 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 (see section 5.3).

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.

Some clinical studies suggest that metformin can increase ovulation in women with polycystic ovarian syndrome (PCOS). However, there is no evidence to date that metformin increases the number of live births in women with PCOS

4.6 Effects on ability to drive and use machines

For Glimepiride

No studies on the effects on the ability to drive and use machines have been performed.

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

For Metformin

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).

4.7 Undesirable effects

For Glimepiride

The following adverse reactions from clinical investigations were based on experience with glimepiride and other sulfonylureas, were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to< 1/100; rare: ≥1/10,000 to <1/1,000; very rare: < 1/10,000), not known (cannot be estimated from the available data).

<u>Blood and lymphatic system disorders</u>

Rare: thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, erythropenia, haemolytic anaemia and pancytopenia, which are in general reversible upon discontinuation of medication.

Not known: severe thrombocytopenia with platelet count less than 10,000/µl and thrombocytopenic purpura.

<u>Immune system disorders</u>

Very rare: leukocytoclastic vasculitis, mild hypersensitivity reactions that may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock.

Not known: cross-allergenicity with sulfonylureas, sulfonamides or related substances is possible.

<u>Metabolism and nutrition disorders</u> Rare: hypoglycaemia.

These hypoglycaemic reactions mostly occur immediately, may be severe and are not always easy to correct. The occurrence of such reactions depends, as with other hypoglycaemic therapies, on individual factors such as dietary habits and dosage (see further under section 4.4). <u>Eye disorders</u>

Not known: visual disturbances, transient, may occur especially on initiation of treatment, due to changes in blood glucose levels.

<u>Gastrointestinal disorders</u>
Rare: dysgeusia

Very rare: nausea, vomiting, diarrhoea, abdominal distension, abdominal discomfort and abdominal pain, which seldom lead to discontinuation of therapy.

<u>Hepato-biliary disorders</u>
Not known: hepatic enzymes increased.

Very rare: hepatic function abnormal (e.g. with cholestasis and jaundice), hepatitis and hepatic failure.

<u>Skin and subcutaneous tissue disorders</u>

<u>Rare: alopecia</u>

Not known: hypersensitivity reactions of the skin may occur as pruritus, rash, urticaria and photosensitivity.

<u>Investigations</u> Rare: weight gain

Very rare: blood sodium decrease

For Metformin

In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with metformin prolonged-release tablets was similar in nature and severity to that

reported in patients treated with metformin immediate release tablets.

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

The following adverse reactions may occur under treatment with metformin.

Frequencies are defined as follows: very common: ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 to <1/100; rare ≥1/10,000 to <1/1,000; very rare <1/10,000.

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

<u>Metabolism and nutrition disorders</u>

Very rare: Lactic acidosis (see section 4.4).

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.

<u>Nervous system disorders</u>

Common: Altered Taste

<u>Gastrointestinal disorders</u> *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.

<u>Hepatobiliary disorders</u>

Very rare

• Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

<u>Skin and subcutaneous tissue disorders</u> Very rare

• Skin reactions such as erythema, pruritus, urticarial

4.8 Overdose

For Glimepiride

Symptoms

After ingestion of an overdosage hypoglycaemia may occur, lasting from 12 to 72 hours, and may recur after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in hospital is recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycaemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, co-ordination problems, sleepiness, coma and convulsions.

Management

Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium-sulphate (laxative). If large quantities have been ingested gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) overdosage hospitalisation in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic.

Paediatric population

In particular, when treating hypoglycaemia due to accidental intake of glimepiride in infants and young children, the dose of glucose given must be carefully controlled to avoid the possibility of producing dangerous hyperglycaemia. Blood glucose should be closely monitored.

For 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

For Glimepiride

Pharmacotherapeutic group: Oral blood glucose lowering drugs: Sulfonamides, urea derivatives.
ATC Code: A10B B12.
Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group. It may be used in noninsulin dependent diabetes mellitus.

Mechanism of action

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells.

As with other sulphonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulphonylureas.

Insulin release

Sulphonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane.

Closing the potassium channel induces depolarisation of the beta cell and results -by opening of calcium channels - in an increased influx of calcium into the cell.

This leads to insulin release through exocytosis.

Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel but which is different from the usual sulphonylurea binding site.

Extrapancreatic activity

The extrapancreatic effects are for example an improvement of the sensitivity of the peripheral tissue for insulin and a decrease of the insulin uptake by the liver.

The uptake of glucose from blood into peripheral muscle and fat tissues occurs via special transport proteins, located in the cells membrane. The transport of glucose in these tissues is the rate limiting step in the use of glucose. Glimepiride increases very rapidly the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose uptake.

Glimepiride increases the activity of the glycosyl-phosphatidylinositol-specific phospholipase C which may be correlated with the drug-induced lipogenesis and glycogenesis in isolated fat and muscle cells.

Glimepiride inhibits the glucose production in the liver by increasing the intracellular concentration of fructose-2,6-bisphosphate, which in its turn inhibits the gluconeogenesis.

General

In healthy persons, the minimum effective oral dose is approximately 0.6 mg. The effect of glimepiride is dose-dependent and reproducible. The physiological response to acute physical exercise, reduction of insulin secretion, is still present under glimepiride.

There was no significant difference in effect regardless of whether the drug was given 30 minutes or immediately before a meal. In diabetic patients, good metabolic control over 24 hours can be

achieved with a single daily dose.

Although the hydroxy metabolite of glimepiride caused a small but significant decrease in serum glucose in healthy persons, it accounts for only a minor part of the total drug effect.

Combination therapy with metformin.

Improved metabolic control for concomitant glimepiride therapy compared to metformin alone in patients not adequately controlled with the maximum dosage of metformin has been shown in one study.

Combination therapy with insulin

Data for combination therapy with insulin are limited. In patients not adequately controlled with the maximum dosage of glimepiride, concomitant insulin therapy can be initiated. In two studies, the combination achieved the same improvement in metabolic control as insulin alone; however, a lower average dose of insulin was required in combination therapy.

Special populations

Paediatric population:

An active controlled clinical trial (glimepiride up to 8 mg daily or metformin up to 2,000 mg daily) of 24 weeks duration was performed in 285 children (8-17 years of age) with type 2 diabetes.

Both glimepiride and metformin exhibited a significant decrease from baseline in HbA1c (glimepiride-0.95 (se 0.41); metformin -1.39 (se 0.40)). However, glimepiride did not achieve the criteria of non-inferiority to metformin in mean change from baseline of HbA1c. The difference between treatments was 0.44% in favour of metformin. The upper limit (1.05) of the 95% confidence interval for the difference was not below the 0.3% non-inferiority margin.

Following glimepiride treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are available in paediatric patients.

For Metformin

Pharmacotherapeutic group: Drugs used in diabetes; blood glucose lowering drugs, excl. insulins, ATC code: A10BA02.

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.

Mechanism of action

Metformin may act via 3 mechanisms:

(1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis;

(2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation;

(3) 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 (GLUT).

Pharmacodynamic effects

In clinical studies, the major non-glycaemic effect of metformin is either weight stability or modest weight loss.

In humans, independently of its action on glycaemia, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged-release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

Clinical efficacy and safety

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in overweight type 2 diabetic patients treated with immediate release

metformin as first-line therapy after diet failure. 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 patientyears), p=0.0023, and versus the combined sulphonylurea 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 sulphonylurea 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 sulphonylurea, 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.

5.2 **Pharmacokinetic** properties

For Glimepiride

Absorption

The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations (Cmax) are reached approx. 2.5 hours after oral intake (mean 0.3 µg/ml during multiple dosing of 4 mg daily) and there is a linear relationship between dose and both C max and AUC (area under the time/concentration curve).

Distribution

Glimepiride has a very low distribution volume (approx. 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (>99%), and a low clearance (approx. 48 ml/min).

In animals, glimepiride is excreted in milk. Glimepiride is transferred to the placenta. Passage of the blood brain barrier is low.

Biotransformation and elimination

Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.

After a single dose of radio labelled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites -most probably resulting from hepatic metabolism (major enzyme is CYP2C9)- were identified both in urine and faeces: the hydroxy derivative and the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of these metabolites were 3 to 6 and 5 to 6 hours respectively.

Comparison of single and multiple once-daily dosing revealed no significant differences in pharmacokinetics, and the intra individual variability was very low. There was no relevant accumulation.

Special Populations

Elderly people

Pharmacokinetics were similar in males and females, as well as in young and elderly (above 65 years) patients.

Renal impairment

In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for average serum concentrations to decrease, most probably resulting from a more rapid elimination because of lower protein binding. Renal elimination of the two metabolites was impaired. Overall no additional risk of accumulation is to be assumed in such patients.

Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

Paediatric population

A fed study investigating the pharmacokinetics, safety, and tolerability of a 1 mg single dose of glimepiride in 30 paediatric patients (4 children aged 10-12 years and 26 children aged 12-17 years) with type 2 diabetes showed mean AUC (0-last) , Cmax and t1/2 similar to that previously observed in adults.

For Metformin
Absorption

After an oral dose of the prolonged-release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T at 7 hours (T for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, Cmax and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000 mg of metformin prolonged-release tablets is similar to that observed after administration of 1000 mg of metformin immediate release tablets b.i.d.

Intrasubject variability of C max and AUC of metformin prolonged-release is comparable to that observed with metformin immediate release tablets.

When the prolonged-release tablet is administered in fasting conditions the AUC is decreased by 30% (both C and T are unaffected).

Mean metformin absorption from the prolonged-release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000mg of metformin as prolonged-release tablets.

Following a single oral administration in the fed state of one tablet of Metformin 1000mg

prolonged-release tablets, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours).

Metformin 1000mg prolonged-release tablets were shown to be bioequivalent to Metformin 500mg prolonged-release tablets at a 1000mg dose with respect to C and AUC in healthy fed and fasted subjects.

When the 1000mg prolonged-release tablet is administered in fed conditions the AUC is increased by 77% (C is increased by 26% and T is slightly prolonged by about 1 hour).

<u>Distribution</u>

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.

<u>Biotransformation</u>

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

<u>Elimination</u>

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.

<u>Characteristics in specific groups of patients</u>

 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).

5.3 Preclinical safety data

For Glimepiride

Preclinical effects observed occurred at exposures sufficiently in excess of the maximum human exposure as to indicate little relevance to clinical use, or were due to the pharmacodynamic action (hypoglycaemia) of the compound. This finding is based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproduction toxicity studies. In the

latter (covering embryotoxicity, teratogenicity and developmental toxicity), adverse effects observed were considered to be secondary to the hypoglycaemic effects induced by the compound in dams and in offspring.

For Metformin

Absorption

After an oral dose of the prolonged-release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T at 7 hours (T for the immediate
release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, C and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000 mg of metformin prolonged-release tablets is similar to that observed after administration of 1000mg of metformin immediate release tablets b.i.d.

Intrasubject variability of C and AUC of metformin prolonged-release is comparable to that observed with metformin immediate release tablets.

When the prolonged-release tablet is administered in fasting conditions the AUC is decreased by 30% (both C and T are unaffected).

Mean metformin absorption from the prolonged-release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000mg of metformin as prolonged-release tablets.

Following a single oral administration in the fed state of one tablet of Metformin 1000mg prolonged-release tablets, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours).

Metformin 1000mg prolonged-release tablets were shown to be bioequivalent to Metformin 500mg prolonged-release tablets at a 1000mg dose with respect to C and AUC in healthy fed
and fasted subjects.

When the 1000mg prolonged-release tablet is administered in fed conditions the AUC is increased by 77% (C is increased by 26% and T is slightly prolonged by about 1 hour).

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 Vd ranged between 63-

276 L.

Biotransformation

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxy propyl methyl cellulose

Sodium CMC

Povidone K-30

Colloidal silicon dioxide

Magnesium sterate

Lactose monohydrate

Sodium starch glycolate Type A

Iron oxide yellow

Iron oxide red, Polysorbate 80

Microcrystalline cellulose PH 102

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4   Special precautions for storage

Store below 30°C. Protect from light and moisture. Keep out of reach of children.

6.5   Nature and contents of container

Alu - PVC/PVDC blister pack of 10 Tablets. Pack size: 3 x 10's

6.6   Special precautions for disposal and other handling

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

POM	PP	Schedule 2	NS2

7   MARKETING AUTHORISATION HOLDER

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10. DATE OF REVISION OF THE TEXT

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