SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

INSUFOR 500 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each film coated tablet contains 500 mg metformin hydrochloride.

Excipients:

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

White colored, round, biconvex film coated tablets.

4. CLINICAL PROPERTIES

4.1 Therapeutic indications

INSUFOR is indicated for the treatment of type 2 diabetes mellitus, especially when dieting and exercise alone are insufficient to control blood sugar in overweight patients.

- INSUFOR could be used in adults separately or combined with other oral antidiabetics or insulin.
- INSUFOR could be used in adolescents and children over 10 years of age separately or combined with insulin.

Only after the diet was inadequate, diabetic complications were reduced in overweight adult patients with type 2 diabetes treated with metformin as first-line treatment. (See section 5.1)

4.2 Posology and method of administration

Posology/ frequency and duration of administration:

In adults:

Monotherapy and combination with other oral antidiabetic agents

The usual starting dose is 1 tablet INSUFOR 500 mg or 850 mg metformin hydrochloride 2 or 3 times daily given during or after meals.

After 10 to 15 days the dose should be adjusted on the basis of blood glucose levels. A slow increase of dose may improve gastrointestinal tolerability.

In patients receiving a high metformin dose (2 to 3 grams per day), it is possible to replace two INSUFOR 500 mg film coated tablets with one INSUFOR 1000 mg film coated tablet.

The maximum recommended dose of metformin is 3 g daily, taken as 3 divided doses.

If transfer from another oral antidiabetic agent is intended; it should be discontinued the other medicine and initiate metformin hydrochloride at the dose indicated above.

Combination with insulin

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

Administration method:

INSUFOR is used orally with meals or after meals with a glass of water.

Additional information about special population:

Liver/ Renal failure:

Correspondingly decreasing of creatine clearance, half-life of INSUFOR in plasma and blood prolongs and renal clearance decreases. This creates to increase the plasma concentration of medicine. Therefore, INSUFOR should not be used in men patients that have above 1.5 mg/dl of serum creatine level and in women patients that have above 1.4 mg/dl (see Section 4.3)

INSUFOR should not be used in liver failure patients because liver infection is a risk factor for lactic acidosis improvement during INSUFOR treatment (see Section 4.3).

Pediatric population:

INSUFOR can be used in children from 10 years of age and adolescents.

Dosage in these age groups patients:

Monotherapy and combination with insulin

• The standard 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 max. 2 or 3 divided doses.

Geriatric population:

Due to the potential for decreased renal function in elderly subjects, the metformin hydrochloride dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see Section 4.4).

4.3 Contraindications

It is contraindicated;

- In the hypersensitivity to metformin or to any of the excipients.
- In the diabetic ketoacidosis, diabetic pre-coma and metabolic acidosis
- Renal failure or renal dysfunction (KI_{kr} < 60 ml/min). (serum creatine level >1.5 mg/dl in men, >1.4 mg/dl in women, or abnormal creatine clearance)
- In the acute conditions with the potential to alter renal function like intravascular administration of iodized concentration substances that results to dehydration, severe infection, shock, lactic acidosis (see Section 4.4)
- In the acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, septicemia, shock.
- In hepatic insufficiency, acute alcohol intoxication, alcoholism.
- In lactation

4.4 Special warnings and precautions for use

Lactic acidosis:

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis:

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia.

Lactic acidosis is characterized with acidotic dyspnea, abdominal pain, hypothermia and coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l, an increased anion gap and an increased lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalized immediately (see Section 4.9).

Doctors should warn patients about lactic acidosis risk and symptoms.

Renal functions:

As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels by using the Cockcroft-Gault formula) should be determined before initiating treatment and regularly thereafter:

• At least annually in patients with normal renal function,

• At least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should

be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).

Administration of iodinated contrast media:
The intravascular administration of iodinated contrast media in radiologic studies can lead to renal failure. This may lead to metformin accumulation and may cause to lactic acidosis. Using of Metformin must be discontinued prior to, or at the time of the administration and it should be started until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.5).

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

Children and adolescents:
The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin hydrochloride 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 study conducted in children and adolescents. Although efficacy and safety of metformin in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

Other precautions:

All patients should be administrated a diet with regular distribution of carbohydrate 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 hypoglycemia. But caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended combinations

Alcohol:

In acute alcohol intoxication, risk of lactic acidosis increases particularly in the following cases:

- Fasting or malnutrition,
- Liver failure.

It should avoid consumption of alcohol and alcohol-containing medicines when this drug is used.

Iodinated contrast media:

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

Using of Metformin must be discontinued prior to 48 hours the administration of iodinated contrast media by intravascularly or during the administration, and it should be restarted 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see Section 4.4).

<u>Medicines to take into consideration in concomitant use</u>

Medicinal products with intrinsic hyperglycemic activity [e.g. glucocorticoids (systemic and local routes) and sympathomimetics]:

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective

medicinal product and upon its discontinuation.

Diuretics, especially loop diuretics:

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

ACE inhibitors:

ACE inhibitors may decrease the blood glucose level, so metformin dose should be adjusted during treatment with the other medicine and after adding the other medicine or quitting.

Addition information about special population:

There is no information.

Pediatric population:

There is no information.

4.6 Pregnancy and lactation

General advice:

Pregnancy category: B

Women of childbearing potential/ Birth control (Contraception)

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 fetus.

Pregnancy period

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 indicates an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or fetal 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 fetus.

Lactation period

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, considering the benefit of breast-feeding and the potential risk to adverse effects on the child.

Reproductive ability/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. For this reason, it is thought that it will not cause harmful effects on reproductive ability and fertility in humans.

4.7 Effects on ability to drive and use machines

Metformin monotherapy does not cause hypoglycemia. Therefore, has no effect on the ability to drive or to use machines.

However, patients that drive and use machines should be alerted to the risk of hypoglycemia when metformin is used in combination with other antidiabetic agents (e.g. sulfonylureas, insulin or meglitinides).

4.8 Undesirable effects

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhea, abdominal pain and loss of appetite. These disappear spontaneously in most cases. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to increase slowly the doses.

The heavy complication such as lactic acidosis may emerge rarely (see Section 4.4).

The following adverse reactions may improve under the metformin treatment. Frequencies about undesirable effects are defined as this:

Very common: (≥ 1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), unknown (cannot be estimated from the available data).

Blood and lymphatic system disorders

Very rare: Blood coagulation disorder, hemolytic anemia.

Metabolism and nutrition disorders

Very rare: Lactic acidosis that manifest itself with vomiting, muscle cramp, stomach ache, asthenia, feeling bad, difficulty of breath taking (see section 4.4). Decrease of vitamin B12 absorption and decrease of serum levels during long-term use of metformin, it is advisable to consider this etiology when referring to megaloblastic anemia, loss of weight and marasmus (cachexia), loss of appetite (anorexia). Low blood sugar than normal that manifest itself with trembling, diaphoresis, pins and needles in mouth and tongue, paleness, tachycardia and disturbance (hypoglycemia).

Nervous system disorders

Common: Taste disturbance (metallic taste in mouth), asthenia, dizziness and drowsiness, headache.

Gastrointestinal disorders

Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhea, abdominal pain, abdominal discomfort, flatulence, dyspepsy, malabsorption and loss of appetite. These undesirable effects occur usually in the initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in divided to 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve

gastrointestinal tolerability.

Hepatobiliary disorders

Very rare: Isolated reports related to liver function tests abnormalities or hepatitis; (is liver inflammation, exhaustion, loss of appetite, loss of weight, yellowing of skin and eyes in white parts), these improve upon metformin discontinuation. Cholestatic hepatitis; is characterized condition with hepatitis, light colored stools, itching, asthenia, anorexia. Increasing of liver enzyme level.

Skin and subcutaneous tissue disorders

Very rare: Skin reactions such as lichen planus, skin rash, erythema, pruritus, urticaria

Additional information about special population:

Pediatric population:

The reported adverse effects in published and post marketing data and in controlled clinical studies in a limited pediatric population aged 10-16 years treated during 1 year, is similar in content and severity according to the reported in adults.

4.9 Overdose and its treatment

Hypoglycemia has not been seen with metformin hydrochloride doses of up to 85 g, although the occurrence of lactic acidosis in certain 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 hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamical properties

Pharmacotherapeutic group: Blood glucose lowering drugs. Biguanides;

ATC code: A10BA02

Mechanism of action:
Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia.

Metformin may act via 3 mechanisms below:
1) It reduces hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
2) It improves peripheral glucose uptake and utilization by increasing insulin sensitivity in muscle.
3) It delays intestinal glucose absorption.
Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.
Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.
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 favorable 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 randomized study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes.

The obtained results for overweight patients treated with metformin after failure of diet alone is shown below:

- A significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 cases/1000 patient-years) versus diet alone (43.3 cases/1000 patient-

years), p=0.0023, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 cases/1000 patient-years), p=0.0034;

- A significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 cases/1000 patient-years, diet alone 12.7 cases/1000 patient-years, p=0.017;

- A significant reduction of the absolute risk of overall mortality: metformin 13.5 cases/1000 patient-years versus diet alone 20.6 cases/1000 patient-years (p=0.011), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 cases/1000 patient-years (p=0.021);

- A significant reduction in the absolute risk of myocardial infarction: metformin 11 cases/1000 patient-years, diet alone 18 cases/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.

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

5.2 Pharmacokinetic properties

General properties

Absorption:

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

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

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

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

Disintegration:

Binding to plasma protein is negligible. Metformin disperses into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (V_d) ranged 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 of metformin is decreased in proportion to that of creatinine clearance and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Linearity/Non-linear condition:

It is thought that metformin absorption pharmacokinetic is not linear.

Characteristic properties in patients:

Pediatric population:

Single dose study: After single doses of metformin hydrochloride 500 mg pediatric 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 pediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC_{0-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 glycemic control, this is of limited clinical relevance.

5.3 Preclinical safety data

Data of preclinical animal studies obtained from clinical studies based on reliability pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity of medicine, no reveal obvious danger for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet content:

Kollidon CL

Pregelatinized Maize Starch

Povidone K-30

Povidone K-90

Magnesium stearate
Purified water

Film-coating content:
Polyvinyl alcohol
Talc
Polyethylene glycol
Titanium dioxide
Purified Water

6.2 Incompatibilities

There is no known incompatibility.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C at room temperature.

6.5 Nature and contents of container

In box, Alu-PVC/PVDC blister (90 tablets)

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

World Medicine Ilac Sanayi ve Tic. A.Ş.
Bağcılar, Istanbul, Turkey

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorization date:

Renewal authorization date:

10. DATE OF REVISION OF THE TEXT