Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metformin Pensa 1000 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1000 mg metformin hydrochloride corresponding to 780 mg metformin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, biconvex, oval shaped film-coated tablets with ‘A’ debossed on one side and ‘62’ debossed on the other side. The tablets have a non-functional groove and therefore cannot be broken.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycemic control.

- In adults, Meformin Pensa film-coated tablets may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.

- In children from 10 years of age and adolescents, Metformin Pensa film-coated tablets 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 hydrochloride as first-line therapy after diet failure (see section 5.1).

4.2 Posology and method of administration

Adults:
Monotherapy and combination with other oral antidiabetic agents:
- The usual starting dose is 500mg or 850mg 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 measurements. A slow increase of dose may improve gastrointestinal tolerability.

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

If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate metformin hydrochloride at the dose indicated above.

Combination with insulin:
Metformin hydrochloride and insulin may be used in combination therapy to achieve better blood glucose control. Metformin hydrochloride is given at the usual starting dose of 500mg or 850mg metformin hydrochloride 2or3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Elderly:
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).

Children and adolescents:
Monotherapy and combination with insulin

- Metformin Pensa film-coated tablets 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 meals 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.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (creatinine clearance < 60 ml/min).
- Acute conditions with the potential to alter renal function such as:
  dehydration,
  severe infection,
  shock,
  intravascular administration of iodinated contrast agents (see section 4.4).
- Acute or chronic disease which may cause tissue hypoxia such as:
  cardiac or respiratory failure,
  recent myocardial infarction,
  shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- 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 hydrochloride accumulation. Reported cases of lactic acidosis in patients on metformin hydrochloride 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 characterised by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin hydrochloride should be discontinued and the patient should be hospitalised immediately (see section 4.9).

Renal function:
As metformin hydrochloride is excreted by the kidney, serum creatinine levels 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 diueretic therapy and when starting therapy with a non-steroidal
anti-inflammatory drug.

Administration of iodinated contrast agent:
As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin hydrochloride 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 (see section 4.5).

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

Paediatric population:
The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin hydrochloride is initiated.

No effect of metformin hydrochloride 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 hydrochloride on these parameters in metformin hydrochloride-treated children, especially pre-pubescent 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 hydrochloride in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

Other precautions:
All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet. The usual laboratory tests for diabetes monitoring should be performed regularly.
Metformin hydrochloride alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or sulfonylureas.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended
Alcohol:
Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:
fasting or malnutrition;
hepatic insufficiency.
Avoid consumption of alcohol and alcohol-containing medicinal product.

Iodinated contrast agents (see section 4.4):
Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin hydrochloride accumulation and an increased risk of lactic acidosis.

Metformin hydrochloride 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.

Combinations requiring precautions for use:
Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic medicinal product during therapy with the other medicinal product and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. Therefore, dose adjustment of metformin hydrochloride may be necessary during and after addition or discontinuation of such medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy
To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or fetal development, parturition or postnatal development (see section 5.3).

When a woman plans to become pregnant and during pregnancy, diabetes should not be treated with metformin hydrochloride but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of fetal malformations associated with abnormal blood glucose levels.

Breastfeeding
Metformin hydrochloride is contra-indicated during lactation.
Meformin hydrochloride is excreted into milk in lactating rats. Similar data are not available in humans and a decision should be made whether to discontinue breast-feeding or to discontinue metformin hydrochloride, taking into account the importance of the medicinal product to the mother.

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.

4.7 Effects on ability to drive and use machines

Metformin hydrochloride monotherapy does not cause hypoglycaemia and therefore has no influence on the ability to drive and use machines.

However, patients should be alerted to the risk of hypoglycaemia when meformin hydrochloride is used in combination with other antidiabetic agents (sulfonylureas, insulin, repaglinide).

4.8 Undesirable effects

The following undesirable effects may occur under treatment with metformin hydrochloride. 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)
not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Metabolism and nutrition disorders:
Very rare: Lactic acidosis (see section 4.4.).

Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin hydrochloride. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

Nervous system disorders:
Common: Taste disturbance

Gastrointestinal disorders:
Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin hydrochloride 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:
Not known: Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin hydrochloride discontinuation.
In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

Skin and subcutaneous tissue disorders:
Very rare: Skin reactions such as erythema, pruritus and urticaria.

4.9 Overdose

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 hydrochloride 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 hydrochloride is haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood Glucose lowering drugs, excl Insulins, Biguanides, ATC code: A10BA02

Metformin hydrochloride 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 hydrochloride 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 utilization
3) and delay of intestinal glucose absorption.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin hydrochloride increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy and safety
The prospective randomised (UKPDS) study 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 hydrochloride after failure of diet alone showed:
a significant reduction of the absolute risk of any diabetes-related complication in the metformin hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride used as second-line therapy, in combination with a sulfonylurea.

In type 1 diabetes, the combination of metformin hydrochloride and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

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

5.2 Pharmacokinetic properties

Absorption
After an oral dose of metformin hydrochloride, T_{max} is reached in 2.5 hours. 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 hydrochloride absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin hydrochloride absorption is non-linear.

At the recommended metformin hydrochloride doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin hydrochloride plasma levels (C_{max}) did not exceed 4 microgram/ml, even at maximum doses.

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

Distribution
Plasma protein binding is negligible. Metformin hydrochloride 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.

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

Elimination
Renal clearance of metformin hydrochloride is >400 ml/min, indicating that metformin hydrochloride 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 hydrochloride in plasma.

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

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (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 glycaemic control, this is of limited clinical relevance.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Povidone
Magnesium stearate

Film-coating:
Hypromellose 5cP
Macrogol 400
Macrogol 6000

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

20 or 60 film-coated tablets in blister packs (PVC / aluminium), each blister containing 10 film-coated tablets.

Not all pack sizes may be marketed.

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.

7 MARKETING AUTHORISATION HOLDER

Pensa Pharma AB
Birger Jarlsgatan 22
114 34 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER

PA 1647/8/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 30th March 2012

9 DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

10 DATE OF REVISION OF THE TEXT

September 2012