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1.3.1 spc-label-pl - common-spc - 2,421 (DE/H/1806-1808/001 - harmonized texts)		20130708
METFORMIN HYDROCHLORIDE 1 G FILM-COATED TABLET		722-1268.00

1. NAME OF THE MEDICINAL PRODUCT

Metformin 1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

white, oval, biconvex film-coated tablets, scored, marked „M 1G“ on one side

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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 glycaemic control.

- In adults, metformin 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 may be used as monotherapy or in combination with insulin.

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

4.2 Posology and method of administration

A dose of 850 mg is not possible with Metformin 1000 mg. Another appropriate formulation should be used for a dose of 850 mg.

Adults

Monotherapy and combination with other oral antidiabetic agents

The usual starting dose is 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 measurements. A slow increase of dose may improve the gastro-intestinal tolerability.

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

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, the other agent should be discontinued and metformin initiated at the dose indicated above.

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Combination with insulin

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

Elderly

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

Paediatric population

Monotherapy and combination with insulin

Metformine 1000 mg film-coated tablet can be used in children from 10 years of age and adolescents. The usual starting dose is 500 mg or 850 mg metformin hydrochloride once daily, given during or after meals.

After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin hydrochloride is 2 g daily, taken as 2 or 3 divided doses.

4.3 Contraindications

- Hypersensitivity to metformin 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) (see section 4.4).
- Acute conditions with the potential to alter renal function such as
 - dehydration
 - severe infection
 - shock
- Acute or chronic diseases which may cause tissue hypoxia such as
 - cardiac or respiratory failure
 - recent myocardial infarction
 - shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.

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 characterised by acidotic dyspnoea, abdominal pain and hypothermia, followed by coma. Diagnostic laboratory findings include decreased blood pH, plasma lactate levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalised immediately (see section 4.9).

Renal function:

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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 creatinine clearance level at the lower limit of normal and in elderly patients.

Decreased renal function in elderly patients is frequent and asymptomatic special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy, diuretic therapy or when starting therapy with a non-steroidal anti-inflammatory drug (see section 4.3).

Administration of iodinated contrast agents

The intravascular administration of iodinated contrast agents in radiologic studies can lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. Metformin must be discontinued prior to, or at the time of the test and not be re-instituted 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 prior to elective surgeries 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 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 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 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 alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended:

Alcohol

Acute alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of:

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- fasting or malnutrition;
- hepatic insufficiency.

Avoid consumption of alcohol and alcohol-containing medicinal products.

Iodinated contrast agents

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

Metformin must be discontinued prior to or at the time of the test and not be re-instituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.4).

Combinations requiring precautions for use:

- *Medicinal products with intrinsic hyperglycaemic activity as glucocorticoids (systemic or by local route) and sympathomimetics.*
More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during the therapy with the respective medicinal products and upon its discontinuation.
- *Diuretics especially loop diuretic*
They may increase the risk of lactic acidosis due to their potential to decrease renal function.

4.6 Fertility, pregnancy and lactation

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.

Breastfeeding

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding 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.

4.7 Effects on ability to drive and use machines

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 (sulphonylureas, insulin or

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meglitinides).

4.8 Undesirable effects

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve 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 following adverse reactions may occur under treatment with metformin.

Frequencies are defined as follows: very common: $\geq 1/10$; common $\geq 1/100$, $< 1/10$; uncommon $\geq 1/1,000$, $< 1/100$; rare $\geq 1/10,000$, $< 1/1,000$; very rare $< 1/10,000$, not known (cannot be estimated from the available data).

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. 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 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 discontinuation.

Skin and subcutaneous tissue disorders:

Very rare: Skin reactions such as erythema, pruritus, urticaria

Paediatric population

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.

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 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 from the body is haemodialysis.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood glucose lowering drugs, excl. insulines. Biguanides
ATC code: A10BA02

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial blood glucose levels. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin probably acts via three 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) 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 (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 favourable effects on lipid metabolism. This has been demonstrated at therapeutic doses in controlled, medium-term or long-term clinical studies: Metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy:

A prospective randomised study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes.

Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years), $p=0.0023$, and versus the combined 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 versus 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 of the absolute risk of myocardial infarction: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patient-years ($p=0.01$).

Benefit regarding clinical outcome has not been shown for metformin when used as second-line therapy in combination with a sulphonylurea.

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 established.

Paediatric population

Controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year

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

5.2 Pharmacokinetic 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 non-linear.

At the recommended metformin 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 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 peak plasma 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.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63-276 l.

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 decreases in proportion to that of creatinine and thus the apparent elimination half-life is prolonged, leading to increased concentrations of metformin in plasma.

Paediatric population

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

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily (BID) 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 BID for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

5.3 Preclinical safety data

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

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Povidone K 90

Magnesium stearate

Film coating:

Hypromellose

Macrogol 4000

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister:

Film-coated tablets are packed in PVC/aluminium.

Pack sizes: 20, 30, 60, 90 (only for DE/H/1808), 120, 180(only for DE/H/1808), 200(only for DE/H/1808) and 300 film-coated tablets.

Tablet container:

Film-coated tablets are packed in HDPE bottles with **LDPE caps**.

Original packs with 100 and 200 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. Marketing Authorization Holder and Manufacturer

Name: Sandoz GmbH, Kundl

Address: Biochemiestrasse 106250.

Country: Austria.

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Manufacturer

Name: **Lek S.A.**

Company name: **Lek S.A..**

Address: **ul. Podlipie 16, 95-010 Stryków**

Country: **Poland**

8. Marketing Authorization Number

TO BE ALLOCATED

9. Date of First Authorization / Renewal of Authorization

TO BE ALLOCATED

10. Date of revision of the text

04/2014