



COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

**SUMMARY INFORMATION ON A REFERRAL OPINION FOLLOWING AN
ARBITRATION**

PURSUANT TO ARTICLE 11 OF COUNCIL DIRECTIVE 75/319/EEC AS AMENDED, FOR

Glucophage/Glucophage Forte/Risidon/Dianben

International Nonproprietary Name (INN): metformin

BACKGROUND INFORMATION

Glucophage/Glucophage Forte/Risidon/Dianben (metformin) contains the active substance metformin which is an oral antihyperglycaemic agent. Two strengths (500 mg and 850 mg) are registered in all Member States of the European Union, except in Finland where there is only the 500 mg strength and in Greece and Spain, where there is only the 850 mg strength.

In all Member States, national licenses have been originally granted from 1959 to 1997. From these registrations, different Summaries of Product Characteristics have been issued, based on national, divergent decisions. In particular, the therapeutic indications differed significantly.

On 17 May 2000, Lypha Santé acting on behalf of all the Marketing Authorisation Holders presented to the EMEA a referral under Article 11 of Council Directive 75/319/EEC as amended, in order to harmonise the Summaries of Product Characteristics within the Member States. A proposal of Summary of Product Characteristics based on an updated dossier was provided.

The referral procedure started on 29 June 2000. The basis for this arbitration procedure was a harmonisation of the Summaries of Product Characteristics. The CPMP having considered the Rapporteur and the Co-Rapporteur assessment reports, Scientific discussion within the Committee and comments from the Marketing Authorisation Holders, was of the opinion that the benefit/risk ratio of metformin is considered to be favourable for the agreed indications. The CPMP issued a positive opinion, on 19 October 2000, recommending the harmonisation of the Summaries of Product Characteristics for Glucophage/Glucophage Forte/Risidon/Dianben.

An overall summary of the scientific evaluation is provided, together with the amended Summaries of Product Characteristics.

A Decision was issued by the European Commission on 6 February 2001.

SCIENTIFIC CONCLUSIONS

Overall summary of the scientific evaluation of Glucophage/Glucophage Forte/Risidon/Dianben

- Quality issues

The pharmaceutical sections of the Summaries of Product Characteristics (SPCs) have been harmonised, except the sections linked to national marketing authorisations. The proposed shelf-life of 5 years was considered as acceptable.

- Efficacy issues

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. Metformin may act via three mechanisms; by reduction of hepatic glucose production, by increase of insulin sensitivity in muscle/improving peripheral glucose uptake and utilisation and by delaying intestinal glucose absorption.

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism.

The dossier submitted confirms that metformin is indicated in type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Metformin may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in 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 complications in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patients-years), $p=0.0023$, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/1000 patients-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 patients-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 of 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 sulfonylurea, benefit regarding clinical outcome has not been shown.

The documentation to support the use of metformin in type 1 diabetes as an adjuvant to insulin does not fulfill usual requirements for a therapeutic indication and the benefit of addition of metformin in type 1 diabetes has not been established on glycaemic control. However, taking into account some current practice and some data on sparing of insulin when associated to metformin, it should be mentioned in section 5.1 of the SPC that the combination has been used in selected cases of patients.

In line with established practice, slow up-titration of dose may reduce the problem of gastrointestinal intolerance and the maximum dose is 3 g/d when used alone or in combination with other oral agents (or with insulin).

All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

As metformin is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter. Metformin is contraindicated in case of renal failure or renal dysfunction, even moderate, as well as in acute conditions with the potential to alter renal function.

Contraindications also include hepatic insufficiency and acute or chronic disease which may cause tissue hypoxia.

- Safety issues

The incidence of lactic acidosis in diabetics receiving metformin is very low (0.03 cases/1000 patient-years). 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 associated risk factors.

If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalised immediately. As metformin is dialysable, prompt haemodialysis is recommended in patients with lactic acidosis due to metformin, in order to correct the acidosis and remove the accumulated metformin.

The main undesirable effects are gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain and loss of appetite (>10%). Metallic taste has also been reported. A decrease of vitamin B₁₂ serum levels has been observed in patients treated long-term with metformin and appears generally to be without clinical significance (<0.01%).

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

Benefit/Risk considerations

Over 40 years, an extensive experience has been gathered relating to the clinical use and safety of metformin. Based on the documentation submitted by the Marketing Authorisation Holders and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of metformin is favourable for the agreed indications.

GROUNDINGS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- the Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CPMP has recommended the amendment of the Marketing Authorisations for which the Summaries of Product Characteristics are attached.

ANNEX
SUMMARIES OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

GLUCOPHAGE 500 mg film-coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains metformin hydrochloride 500 mg corresponding to metformin base 390 mg

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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. GLUCOPHAGE may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin. A reduction of diabetic complications has been shown in overweight type 2 diabetic patients treated with metformin as first-line therapy after diet failure (see 5.1. Pharmacodynamic properties).

4.2. Posology and method of administration

Monotherapy and combination with other oral antidiabetic agents

- The usual starting dose is one tablet 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 is 3 g daily.
- If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate metformin at the dose indicated above.

Combination with insulin

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin is given at the usual starting dose of one tablet 2-3 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 subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4).

Children: In the absence of data, GLUCOPHAGE should not be used in children.

4.3. Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (e.g., serum creatinine levels > 135 µmol/L in males and > 110 µmol/L in females).

- Acute conditions with the potential to alter renal function such as:
 - Dehydration,
 - severe infection,
 - shock,
 - intravascular administration of iodinated contrast agents (see 4.4 Warnings and special precautions for use).
- 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 special 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:

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 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:

As metformin 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 diuretic therapy and when starting therapy with an NSAID.

Administration of iodinated contrast agent

As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin should be discontinued prior to, or at the time of the test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery

Metformin hydrochloride should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

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 never causes hypoglycaemia, although 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

Inadvisable combinations

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 medications.

Iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis.

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

Associations 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 drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

4.6. Pregnancy and lactation

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

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

Metformin is excreted into milk in lactating rats. Similar data is not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother.

4.7. Effects on ability to drive and to use machines

GLUCOPHAGE 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 (sulfonylureas, insulin, repaglinide).

4.8. Undesirable effects

- Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite (>10%) are very common: these occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent these gastrointestinal symptoms, 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.
- Metallic taste (3 %) is common
- Mild erythema has been reported in some hypersensitive individuals. The incidence of such effects is regarded as very rare (<0.01%)

- A decrease of vitamin B12 absorption with decrease of serum levels has been observed in patients treated long-term with metformin and appears generally to be without clinical significance (<0.01%).
- Lactic acidosis (0.03 cases/1000 patient-years) is very rare (see 4.4. Warnings and special precautions for use).

4.9. Overdose

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin 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

ORAL ANTI-DIABETICS

(A10BA02: Gastrointestinal tract and metabolism)

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.

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).

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

Clinical efficacy :

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

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

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/ 1000 patient-years) versus diet alone (43.3 events/ 1000 patient-years), $p=0.0023$, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/ 1000 patient-years), $p=0.0034$.
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/ 1000 patient-years, $p=0.017$;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/ 1000 patient-years versus diet alone 20.6 events/ 1000 patient-years ($p=0.011$), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/ 1000 patient-years ($p=0.021$);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/ 1000 patient-years, diet alone 18 events/ 1000 patient-years ($p=0.01$)

For metformin used as second-line therapy, in combination with a sulfonylurea, 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

Absorption:

After an oral dose of metformin, T_{max} is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin 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 usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. 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 decreases 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 V_d ranged between 63-276 L

Metabolism:

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

Elimination:

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

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, toxicity reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:

Povidone K 30
magnesium stearate

Film-coat:

Hypromellose

6.2. Incompatibilities

Not applicable

6.3. Shelf-life

5 years

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and contents of the container

6.6. Instructions for use, handling and disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

GLUCOPHAGE/GLUCOPHAGE FORTE/DIANBEN/RISIDON 850 mg film-coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains metformin hydrochloride 850 mg corresponding to metformin base 662,9 mg

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

GLUCOPHAGE/GLUCOPHAGE FORTE/DIANBEN/RISIDON may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

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

4.2. Posology and method of administration

Monotherapy and combination with other oral antidiabetic agents

- The usual starting dose is one tablet 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 is 3 g daily.
- If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate metformin at the dose indicated above.

Combination with insulin

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin is given at the usual starting dose of one tablet 2-3 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 subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4).

Children: In the absence of data, GLUCOPHAGE / GLUCOPHAGE FORTE / DIANBEN / RISIDON should not be used in children.

4.3. Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma.

- Renal failure or renal dysfunction (e.g., serum creatinine levels > 135 µmol/L in males and > 110 µmol/L in females).
- Acute conditions with the potential to alter renal function such as:
 - Dehydration,
 - severe infection,
 - shock,
 - intravascular administration of iodinated contrast agents (see 4.4 Warnings and special precautions for use).
- 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 special 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:

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 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:

As metformin 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 diuretic therapy and when starting therapy with an NSAID.

Administration of iodinated contrast agent

As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin should be discontinued prior to, or at the time of the test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery

Metformin hydrochloride should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

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 never causes hypoglycaemia, although 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

Inadvisable combinations

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 medications.

Iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis.

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

Associations 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 drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation

4.6. Pregnancy and lactation

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

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

Metformin is excreted into milk in lactating rats. Similar data is not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother.

4.7. Effects on ability to drive and to use machines

GLUCOPHAGE / GLUCOPHAGE FORTE / DIANBEN / RISIDON 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 (sulfonylureas, insulin, repaglinide).

4.8. Undesirable effects

- Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite (>10%) are very common : these occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent these gastrointestinal symptoms, 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.
- Metallic taste (3 %) is common.

- Mild erythema has been reported in some hypersensitive individuals. The incidence of such effects is regarded as very rare (<0.01%)
- A decrease of vitamin B12 absorption with decrease of serum levels has been observed in patients treated long-term with metformin and appears generally to be without clinical significance (<0.01%).
- Lactic acidosis (0.03 cases/1000 patient-years) is very rare (see 4.4. Warnings and special precautions for use).

4.9. Overdose

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin 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

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(A10BA02: Gastrointestinal tract and metabolism)

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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).

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

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

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/ 1000 patient-years) versus diet alone (43.3 events/ 1000 patient-years), $p=0.0023$, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/ 1000 patient-years), $p=0.0034$.
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/ 1000 patient-years, $p=0.017$;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/ 1000 patient-years versus diet alone 20.6 events/ 1000 patient-years ($p=0.011$), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/ 1000 patient-years, ($p=0.021$);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/ 1000 patient-years, diet alone 18 events/ 1000 patient-years ($p=0.01$)

For metformin used as second-line therapy, in combination with a sulfonylurea, 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

Absorption:

After an oral dose of metformin, T_{max} is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin 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 usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. 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 decreases 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 V_d ranged between 63-276 L

Metabolism:

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

Elimination:

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

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, toxicity reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:

Povidone K 30
magnesium stearate

Film-coat:

Hypromellose

6.2. Incompatibilities

Not applicable

6.3. Shelf-life

5 years

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and contents of the container

6.6. Instructions for use, handling and disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT