Public Assessment Report

Decentralised Procedure

METFORMIN HYDROCHLORIDE 500MG FILM-COATED TABLETS

METFORMIN HYDROCHLORIDE 850MG FILM-COATED TABLETS

METFORMIN HYDROCHLORIDE 1000MG FILM-COATED TABLETS

Procedure No: UK/H/1962 and 2397/001-3/DC

UK Licence No: PL 32870/0001-3 and 0014-6

USV Europe Limited
LAY SUMMARY

On 18th September 2009, the MHRA granted USV Europe Limited Marketing Authorisations (licences) for the medicinal products Metformin Hydrochloride 500, 850 and 1000mg Film-Coated Tablets (PL 32870/0001-3 and 0014-6). These are prescription-only medicines (POM) that are used for the treatment of non-insulin-dependent diabetes mellitus (type 2 diabetes) in adults and children from 10 years of age.

The active ingredient is metformin hydrochloride, which belongs to a group of medicines called biguanides. Metformin hydrochloride works by lowering high blood sugar levels in patients with diabetes mellitus (type 2 diabetes); particularly in overweight patients when dietary management and exercise alone does not result in control of blood sugar.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Metformin Hydrochloride 500, 850 and 1000mg Film-Coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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## Module 1

| **Product Name** | Metformin Hydrochloride 500mg Film-Coated Tablets  
Metformin Hydrochloride 850mg Film-Coated Tablets  
Metformin Hydrochloride 1000mg Film-Coated Tablets |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<td><strong>Active Substances</strong></td>
<td>Metformin hydrochloride</td>
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<td><strong>Form</strong></td>
<td>Film-coated tablet</td>
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<tr>
<td><strong>Strength</strong></td>
<td>500mg, 850mg or 1000mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>USV Europe Limited, City House, 126 – 130 Hills Road, Cambridge, Cambridgeshire CB2 1RY, United Kingdom.</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
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| **CMS** | UK/H/1962/001-3/DC – Belgium, Czech Republic, Denmark, Finland, Germany, Netherlands, Norway, Poland, Slovak Republic, Spain and Sweden  
UK/H/2397/001-3/DC – Czech Republic, Netherlands and Spain |
| **Procedure Number** | UK/H/1962 and 2397/001-3/DC |
| **Timetable** | Day 210 – 19th August 2009 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Metformin Hydrochloride 500 mg film coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains metformin hydrochloride 500 mg corresponding to metformin base 390 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film coated tablet
White to off white round, biconvex, film coated tablets which are plain on both sides.

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 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 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 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 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 gastrointestinal tolerability. In patients receiving a high metformin 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: 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 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 subjects, the metformin 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 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 metformin hydrochloride or to any of the excipients.
- 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-specified signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia.

Lactic acidosis is characterised by aci"dotic dyspnoea, 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 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 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 hydrochloride 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 (see section 4.5).

Surgery
Metformin hydrochloride should be discontinued 48 hours before elective surgery under general, spinal or peridural anasthesia. 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 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 metformin hydrochloride efficacy and safety in children below 12 did not differ from efficacy and safety in older children, 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 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
Concomitant use not recommended

Alcohol
Increased risk of lactic acidosis in acute alcohol intoxication, particularly in the case of:
- fasting or malnutrition
- hepatic insufficiency

Avoid consumption of alcohol and alcohol-containing medicinal products.

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

Metformin hydrochloride should be discontinued prior to, or at the time of the test and not 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 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 fetal development, parturition or postnatal development (see section 5.3).

When the patient 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.

Metformin hydrochloride is excreted into milk in lactating rats. Similar data are not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin hydrochloride, taking into account the importance of the compound to the mother.
4.7 **Effects on ability to drive and use machines**

Metformin hydrochloride 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 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:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥1/10</td>
</tr>
<tr>
<td>Common</td>
<td>1/100, &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>1/1,000, &lt;1/100</td>
</tr>
<tr>
<td>Rare</td>
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<tr>
<td>Not known</td>
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</table>

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.

Skin and subcutaneous tissue disorders:

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

Metabolism and nutrition disorders:

*Very rare*: 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.

*Very rare*: Lactic acidosis (see section 4.4).

Hepatobiliary disorders:

*Not known*: 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.

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: Oral anti-diabetics.

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.

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 utilisation
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 (GLUT).

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:
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 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)

For metformin hydrochloride 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 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, Tmax 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 are non-linear.

At the usual metformin hydrochloride 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 hydrochloride plasma levels (Cmax) did not exceed 4 μg/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 decreases 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 Vd ranged between 63-276L.

**Metabolism**
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.

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

*Multiple dose study:* Data are restricted to one study. After repeated doses of 500 mg BID for 7 days in paediatric patients the peak plasma concentration (Cmax) and systemic exposure (AUC0-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 toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
**Tablet core**
- Sodium Starch Glycolate (Type A),
- Povidone K-30,
- Maize starch,
- Colloidal Anhydrous Silica,
- Magnesium Stearate

**Tablet coating**
Opadry White 04G58897 containing:
- Hypromellose 15cP, Talc, Titanium Dioxide (E 171), Macrogol 6000, Propylene Glycol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
6.5 Nature and contents of container
The tablets are packed in PVC/aluminium blister packs or in white opaque HDPE container and closure with foil seal induction.

Blister packs: 1 (x100), 9, 10, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 180, 200, 300, 500, 600 or 1000 film coated tablets.

HDPE containers: 10, 20, 21, 30, 40, 50, 56, 60, 90, 100, 120, 180, 200, 300, 400, 500, 600 or 1000 film coated tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal
“Any unused product or waste material should be disposed of in accordance with local requirements”

7 MARKETING AUTHORIZATION HOLDER
USV Europe Limited.
City House, 126 – 130 Hills Road, Cambridge,
Cambridgeshire CB2 1RY, United Kingdom.

8 MARKETING AUTHORIZATION NUMBER(S)
PL 32870/0001
PL 32870/0014

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
18/09/2009

10 DATE OF REVISION OF THE TEXT
18/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Metformin Hydrochloride 850 mg film coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains metformin hydrochloride 850 mg corresponding to metformin base 663 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film coated tablet
White to off white capsule-shaped, biconvex, film coated tablets which are plain on both sides.

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 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 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 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 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 gastrointestinal tolerability. In patients receiving a high metformin 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: 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 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 subjects, the metformin 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 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 metformin hydrochloride or to any of the excipients.
- 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-specified 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 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 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 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 hydrochloride should be discontinued prior to, or at the time of the test and not 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 should be discontinued 48 hours before elective surgery under general, spinal or peridural anasthesia. 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 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 metformin hydrochloride efficacy and safety in children below 12 did not differ from efficacy and safety in older children, 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 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**

**Concomitant use not recommended**

**Alcohol**

Increased risk of lactic acidosis in acute alcohol intoxication, particularly in the case of:
- fasting or malnutrition
- hepatic insufficiency

Avoid consumption of alcohol and alcohol-containing medicinal products.

**Iodinated contrast agents (see section 4.4)**

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

Metformin hydrochloride should be discontinued prior to, or at the time of the test and not 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 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 fetal development, parturition or postnatal development (see section 5.3).

When the patient 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.

Metformin hydrochloride is excreted into milk in lactating rats. Similar data are not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin hydrochloride, taking into account the importance of the compound to the mother.
4.7 Effects on ability to drive and use machines
Metformin hydrochloride 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 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:

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<thead>
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<th>Frequency</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Very common</td>
<td>\geq 1/10</td>
</tr>
<tr>
<td>Common</td>
<td>\geq 1/100, &lt;1/10</td>
</tr>
<tr>
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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.

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

Metabolism and nutrition disorders:
Very rare: 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.

Very rare: Lactic acidosis (see section 4.4).

Hepatobiliary disorders:
Not known: 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.

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: Oral anti-diabetics
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.

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 utilisation
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 (GLUT).

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:
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 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)

For metformin hydrochloride 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 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, Tmax 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 are non-linear.

At the usual metformin hydrochloride 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 hydrochloride plasma levels (Cmax) did not exceed 4 μg/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 decreases 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 Vd ranged between 63-276L.

**Metabolism**
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.

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

*Multiple dose study:* Data are restricted to one study. After repeated doses of 500 mg BID for 7 days in paediatric patients the peak plasma concentration (Cmax) and systemic exposure (AUC0-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 toxicity to reproduction.

6 **PHARMACEUTICAL PARTICULARS**
6.1 **List of excipients**
**Tablet core**
Sodium Starch Glycolate (Type A),
Povidone K-30,
Maize starch,
Colloidal Anhydrous Silica,
Magnesium Stearate

**Tablet coating**
Opadry White 04G58897 containing:
Hypermellose 15cP, Talc, Titanium Dioxide (E 171), Macrogol 6000, Propylene Glycol

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
This medicinal product does not require any special storage conditions.
6.5 Nature and contents of container
The tablets are packed in PVC/aluminium blister packs or in white opaque HDPE container and closure with foil seal induction.

Blister packs: 1 (x100), 9, 10, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 180, 200, 300, 500, 600 or 1000 film coated tablets.

HDPE containers: 10, 20, 21, 30, 40, 50, 56, 60, 90, 100, 120, 180, 200, 300, 400, 500, 600 or 1000 film coated tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal
“Any unused product or waste material should be disposed of in accordance with local requirements”

7 MARKETING AUTHORISATION HOLDER
USV Europe Limited.
City House, 126 – 130 Hills Road, Cambridge,
Cambridgeshire CB2 1RY, United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)
PL 32870/0002
PL 32870/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/09/2009

10 DATE OF REVISION OF THE TEXT
18/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Metformin Hydrochloride 1000 mg film coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains metformin hydrochloride 1000 mg corresponding to metformin base 780 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film coated tablet
White to off white oval shaped, biconvex, film coated tablets, with a deep breakline on one side and a breakline on the other.

The tablet can be divided into equal halves.

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 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 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 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 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 gastrointestinal tolerability. In patients receiving a high metformin 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: 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 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 subjects, the metformin 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 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 metformin hydrochloride or to any of the excipients.
- 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-specified 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 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 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 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 hydrochloride should be discontinued prior to, or at the time of the test and not 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 should 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.

Children and adolescents:
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 metformin hydrochloride efficacy and safety in children below 12 did not differ from efficacy and safety in older children, 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 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
Concomitant use not recommended

Alcohol
Increased risk of lactic acidosis in acute alcohol intoxication, particularly in the case of:
- fasting or malnutrition
- hepatic insufficiency

Avoid consumption of alcohol and alcohol-containing medicinal products.

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

Metformin hydrochloride should be discontinued prior to, or at the time of the test and not 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 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 fetal development, parturition or postnatal development (see section 5.3).

When the patient 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.

Metformin hydrochloride is excreted into milk in lactating rats. Similar data are not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin hydrochloride, taking into account the importance of the compound to the mother.
4.7 Effects on ability to drive and use machines

Metformin hydrochloride 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 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:

<table>
<thead>
<tr>
<th>Frequencies</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Common</td>
<td>1/100, &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>1/1,000, &lt;1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>1/10,000, &lt;1/1,000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Not known</td>
<td>cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

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.

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

Metabolism and nutrition disorders:  
Very rare: 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.

Very rare: Lactic acidosis (see section 4.4).

Hepatobiliary disorders:  
Not known: 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.

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: Oral anti-diabetics.
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.

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 utilisation
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 (GLUT).

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:
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 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)

For metformin hydrochloride 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 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, Tmax 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 are non-linear.

At the usual metformin hydrochloride 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 hydrochloride plasma levels (Cmax) did not exceed 4 μg/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 decreases 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 Vd ranged between 63-276L.

**Metabolism**
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.

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

*Multiple dose study:* Data are restricted to one study. After repeated doses of 500 mg BID for 7 days in paediatric patients the peak plasma concentration (Cmax) and systemic exposure (AUC0-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 toxicity to reproduction.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**
*Tablet core*
Sodium Starch Glycolate (Type A),
Povidone K-30,
Maize starch,
Colloidal Anhydrous Silica,
Magnesium Stearate

*Tablet coating*
Opadry White 04G58897 containing:
Hypermelllose 15cP, Talc, Titanium Dioxide (E 171), Macrogol 6000, Propylene Glycol

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf life**
2 years

**6.4 Special precautions for storage**
This medicinal product does not require any special storage conditions.
6.5 **Nature and contents of container**

The tablets are packed in PVC/aluminium blister packs or in white opaque HDPE container and closure with foil seal induction.

Blister packs: 1 (x100), 9, 10, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 180, 200, 300, 500, 600 or 1000 film coated tablets.

HDPE containers: 10, 20, 21, 30, 40, 50, 56, 60, 90, 100, 120, 180, 200, 300, 400, 500, 600 or 1000 film coated tablets.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**

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

7 **MARKETING AUTHORISATION HOLDER**

USV Europe Limited.
City House, 126 – 130 Hills Road, Cambridge, Cambridgeshire CB2 1RY, United Kingdom.

8 **MARKETING AUTHORISATION NUMBER(S)**

 PL 32870/0003
 PL 32870/0016

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

18/09/2009

10 **DATE OF REVISION OF THE TEXT**

18/09/2009
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER
Metformin 500 mg, 850 mg and 1000 mg film coated tablets
Metformin hydrochloride

The name of your medicine is:
Metformin hydrochloride 500 mg, 850 mg and 1000 mg film coated tablets,
which will be referred to as Metformin tablets throughout the rest of this document.

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Metformin tablets are and what they are used for
2. Before you take Metformin tablets
3. How to take Metformin tablets
4. Possible side effects
5. How to store Metformin tablets
6. Further information

1. WHAT METFORMIN TABLETS ARE AND WHAT THEY ARE USED FOR

Metformin tablets contain the active ingredient metformin hydrochloride. Metformin hydrochloride belongs to a group of medicines called biguanides used for the treatment of non-insulin-dependent diabetes mellitus (type 2 diabetes) in adults and children from 10 years of age.

Insulin is a hormone produced by the pancreas that makes your body take in glucose (sugar) from the blood. Your body uses glucose to produce energy or stores it for future use. If you have diabetes, your pancreas does not make enough insulin or your body is not able to use properly the insulin it produces. This leads to a high level of glucose in your blood. Metformin helps to lower your blood glucose to as normal a level as possible.

Metformin tablets are a medicine used to lower high blood sugar levels in patients with diabetes mellitus (type 2 diabetes), particularly in overweight patients when dietary management and exercise alone does not result in control of blood sugar.

Adults
Your doctor can prescribe Metformin tablets on their own (monotherapy) or in combination with other oral antidiabetic agents, or with insulin.

Children and adolescents
For children from 10 years of age and for adolescents the doctor can prescribe Metformin tablets alone (monotherapy) or in combination with insulin.

2. BEFORE YOU TAKE METFORMIN TABLETS

Do not take Metformin tablets
• if you are allergic (hypersensitive) to metformin hydrochloride or any of the other ingredients of Metformin tablets. (Please refer to Section 6 – Further information).

• if you have uncontrolled diabetes, e.g. severe hyperglycaemia (very high levels of glucose in the blood) or ketoacidosis. Ketoacidosis is a state of health, where substances called ketone bodies accumulate in the blood. Symptoms include stomach pain, fast and deep breathing, sleepiness or unusual fruity odour of the breath.

• if you have kidney problems.

• if your kidney function worsens as a consequence of e.g.
  • loss of too much water (dehydration) due to long-lasting vomiting or severe diarrhoea. Dehydration may lead to kidney problems, which can put you at risk for lactic acidosis (see ‘take special care with Metformin’ below)

• If you have a severe infection, such as infection affecting your lung or bronchial system or your kidney. Severe infection may lead to kidney problems, which can put you at risk for lactic acidosis. (see ‘take special care with Metformin’ below)

• if you have acute or chronic diseases which may lead to reduced amount of oxygen in body tissues (tissue hypoxia) such as
  • heart failure, or difficulties breathing
  • recent heart attack (myocardial infarction)
  • collapse or trauma (shock)

• if you have liver problems, drink a lot of alcohol or suffer from alcoholism

• if you are breast-feeding.

Make sure you ask your doctor for advice, if
• you need to have an examination such as X-ray or scan involving the injection of contrast medicines that contain iodine into your bloodstream
• you need to have surgery

You must stop taking Metformin for a certain period of time before and after the examination or the surgery. Your doctor will decide whether you need any other treatment for this time. It is important that you follow your doctor’s instruction precisely.

Take special care with Metformin tablets

Normal kidney function is essential for treatment with Metformin tablets because of the risk of developing hyperacidity of the blood. This is due to accumulation of lactic acid (lactic acidosis) and is mainly determined by your kidney function. Symptoms of lactic acidosis are vomiting, bellyache (abdominal pain) with muscle cramps, a general feeling of not being well with severe tiredness, and difficulty in breathing. If this happens to you, you may need immediate treatment. Stop taking Metformin immediately and tell your doctor straight away.

Metformin in itself does not lead to hypoglycaemia (insufficient level of blood sugar), but if you take Metformin with other medications for the treatment of diabetes, which can cause hypoglycaemia (e.g. sulfonylureas, insulin) there is a risk of hypoglycaemia. If you experience symptoms of hypoglycaemia such as weakness, dizziness, increased sweating, fast
heart beating, vision disorders or difficulty in concentration, it usually helps to eat or drink something containing sugar.

Using other medicines
If you need to have an injection of contrast medicines that contain iodine into your bloodstream, for example for examinations such as X-ray or scan, you must stop taking Metformin for a certain period of time before and after the examination (see ‘Make sure you ask your doctor for advice’ above).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. During maintenance therapy with Metformin tablets starting or stopping any other medicinal therapy can interfere with your blood sugar control. Please especially inform your doctor or pharmacist if you are taking or have recently taken any of the following medicines:

- corticosteroids (e.g. prednisone)
- specific medicines for the treatment of high blood pressure (ACE inhibitors, e.g. captopril, enalapril)
- medicines which increase urine production (diuretics, e.g. furosemide)
- specific medicines for the treatment of bronchial asthma (β-agonists, e.g. salbutamol)
- iodinated contrast agents
- medicines containing alcohol.

Taking Metformin tablets with food and drink
Drinking alcohol whilst being treated with Metformin tablets increases the possibility of hypoglycaemia (low blood sugar levels) and lactic acidosis. Therefore, you should avoid consumption of alcohol while you are taking Metformin.

Pregnancy and Breast-feeding
Diabetic women who are pregnant or planning to become pregnant should not be treated with Metformin tablets. Instead, insulin should be used to maintain blood glucose levels as close to normal as possible. Inform your doctor if you are pregnant or thinking of becoming pregnant so that he or she can change you to insulin therapy. This medicinal product should not be used while breast-feeding (see section “Do not take Metformin tablets” above). Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Taking metformin alone (monotherapy) does not cause low blood sugar levels (hypoglycaemia) and therefore has no effect on your ability to drive or use machines.
Taking metformin in combination with medicines called sulphonylureas, insulin or other treatments for diabetes may cause low blood sugar levels (with symptoms, such as sweating, fainting, dizziness or weakness) and thus affecting your ability to drive and use machines or work safely. Symptoms of hypoglycaemia include weakness, dizziness, increased sweating, fast heart beat, vision disorders or difficulty in concentration. Do not drive or use machines if you start to feel these symptoms.

3. HOW TO TAKE METFORMIN TABLETS
Always take Metformin tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Metformin cannot replace the benefits of a healthy lifestyle. Continue to follow any advice about diet that your doctor has given you and get some regular exercise.

The dose of Metformin tablets should be determined by the doctor according to your blood sugar levels.

Unless prescribed differently by your doctor, the usual dose is:

**Dosage for adults:**
The usual starting dose is 500 mg or 850mg metformin hydrochloride two or three times a day. The maximum daily dose is 3000 mg metformin hydrochloride, taken as 3 divided doses.

**Dosage for children from 10 years of age and adolescents:**
The usual starting dose is 500 mg 850mg metformin hydrochloride once a day.
The dosage can be increased up to the maximum recommended daily dose of 2000 mg metformin hydrochloride per day, taken as 2 or 3 divided doses. Treatment of children between 10 and 12 years of age is only recommended on specific advice from your doctor, as experience in this age group is limited.

**Monitoring**
- Your doctor will adapt your dose of Metformin to your blood glucose levels. Make sure that you talk to your doctor regularly. This is particularly important for children and adolescents or if you are an older person.
- Your doctor will also check at least once a year how well your kidneys work. You may need more frequent checks if you are an older person or if your kidneys are not working normally.

**How to take Metformin**
Take the tablets during or after meals with an adequate amount of liquid. Do not chew the tablets. When taking 2 or more tablets you should spread them out over the day, e.g. 1 tablet each during or after breakfast and dinner.
Talk to your doctor if you think the dose of Metformin tablets are too high or too low.

**If you take more Metformin tablets than you should**
Inform your doctor immediately if you have taken more tablets than you should have. An overdose of Metformin tablets does not lead to hypoglycaemia but increases the risk of hyperglycaemia of the blood caused by lactic acidosis. Symptoms of early hyperglycaemia are similar to the side effects of metformin on the gastrointestinal tract: sickness, vomiting, diarrhoea and abdominal pain. In severe cases you could also get muscle pain and muscle cramps, very fast breathing which you cannot stop, as well as a clouding of consciousness and coma. This may develop within hours and requires immediate emergency treatment in a hospital.

**If you forget to take Metformin tablets**
If you forget to take Metformin tablets, take the prescribed amount of Metformin tablets at the next prescribed time and try to keep to the prescription in future. Do not take a double dose to make up for a forgotten dose.

**If you stop taking Metformin tablets**
If you stop treatment with Metformin tablets you have to be aware of the risk of uncontrolled blood sugar and of the long-term effects of diabetes mellitus such as damage on eyes, kidneys and blood vessels.
If you have any further questions on the use of this product, ask your doctor or pharmacist.
4. **POSSIBLE SIDE EFFECTS**

Like all medicines, Metformin tablets can cause side effects, although not everybody gets them. Most of the side effects are mild to moderate and will generally disappear after a few days to a few weeks of treatment. Do not be alarmed by this list of possible side effects. You may not experience any of them.

**Other side effects:**

* **Very common (affects more than 1 in 10 people)**
  - upset stomach, feeling sick (nauses), being sick (vomiting), diarrhoea, stomach ache or loss of appetite. These side effects are most likely to happen at the start of treatment. It helps if you spread the doses over the day and if you take the tablets with or straight after a meal. If symptoms continue, stop taking Metformin and talk to your doctor.

* **Common (affects more than 1 in 100 people)**
  - taste of metal in your mouth

* **Very rare (affects fewer than 1 in 10,000 people)**
  - lactic acidosis. This is a very rare but serious complication particularly if your kidneys are not working properly. If you get this complication, you will need immediate treatment. Symptoms of lactic acidosis are vomiting, belly ache (abdominal pain) with muscle cramps, a general feeling of not being well with severe tiredness, and difficulty in breathing. If this happens to you, stop taking Metformin immediately and tell your doctor straight away.
  - skin rash (including redness, itching, laves).
  - low levels of vitmain B12. Over time this may lead to anaemia, a sore mouth or tongue or possibly numbness or tingling in the limbs.

**The frequencies of the following side effects are not known:**

- abnormalities in liver function tests or hepatitis (inflammation of the liver; this may cause tiredness, loss of appetite, weight loss, with or without yellowing of the skin or whites of the eyes). If this happens to you, stop taking this medicine.

**Children and adolescents**

Limited data in children and adolescents showed that adverse events were similar in nature and severity to those reported in adults.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE METFORMIN TABLETS**

Keep out of the reach and sight of children. If a child is teased with Metformin, parents and caregivers are advised to oversee how this medicine is used.

Do not use Metformin tablets after the expiry date stated on the blister and the carton after "EXP".

**Storage conditions**

This medicinal product does not require any special storage conditions.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Metformin tablets contain
The active substance is metformin hydrochloride.
Each film coated tablet contains 500 mg, 850 mg or 1000 mg metformin hydrochloride equivalent to 390 mg, 665 mg, and 780 mg of metformin respectively.

The other ingredients are:
Sodium Starch Glycolate (Type A), Povidone K-30, Maize Starch, Colloidal Anhydrous Silica, Magnesium Stearate, Hypromellose 15cP, Talc, Titanium Dioxide (E 171), Macrogol 6000, Propylene Glycol.

What Metformin tablets looks like and content of the pack
Metformin 500 mg film coated tablets are supplied as white to off white round, biconvex, film coated tablets which are plain on both sides.
Metformin 850 mg film coated tablets are supplied as white to off white capsule shaped, biconvex, film coated tablets which are plain on both sides.
Metformin 1000 mg film coated tablets are supplied as white to off white oval shaped, biconvex, film coated tablets, with a deep breakline on one side and breakline on other side.

Metformin 500 mg, 850 mg and 1000 mg film coated tablets are available in blisters containing 1 (x100), 9, 10, 20, 21, 30, 40, 50, 60, 84, 90, 100, 120, 180, 200, 300, 500, 600 or 1000 film coated tablets or in plastic bottles containing 10, 20, 21, 30, 40, 50, 60, 80, 90, 100, 120, 180, 200, 300, 400, 500, 600 or 1000 film coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
The marketing authorisation holder is USV Europe Limited, City House, 126-130 Hills Road, Cambridge, CB2 1RY, United Kingdom.

Manufacturers
The manufacturer is Accord Healthcare Limited, Sage House, 319 Pinney Road, North Harrow, Middlesex HA1 4HF, United Kingdom.

This medicinal product is authorised in the Member States of the EEA under the following names:

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<tr>
<td>Czech Republic</td>
<td>APO-METFORMIN 500 mg, 850 mg and 1000 mg</td>
</tr>
<tr>
<td>Germany</td>
<td>Metforminhchlorid Orifarm 500 mg, 850 mg, 1000 mg Filmtabletten</td>
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<td>Metformin USV</td>
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<tr>
<td>United Kingdom</td>
<td>Metformin hydrochloride 500 mg, 850 mg and 1000 mg film coated tablets</td>
</tr>
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</table>

This leaflet was last approved on
PAR Metformin Hydrochloride 500, 850 and 1000mg Film-Coated Tablets

PACKAGE LEAFLET: INFORMATION FOR THE USER
Metformin 500 mg, 850 mg and 1000 mg film coated tablets
Metformin hydrochloride

The name of your medicine is:
Metformin hydrochloride 500 mg, 850 mg and 1000 mg film coated tablets,
which will be referred to as Metformin tablets throughout the rest of this document.

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Metformin tablets are and what they are used for
2. Before you take Metformin tablets
3. How to take Metformin tablets
4. Possible side effects
5. How to store Metformin tablets
6. Further information

1. WHAT METFORMIN TABLETS ARE AND WHAT THEY ARE USED FOR

Metformin tablets contain the active ingredient metformin hydrochloride. Metformin hydrochloride belongs to a group of medicines called biguanides used for the treatment of non-insulin-dependent diabetes mellitus (type 2 diabetes) in adults and children from 10 years of age.

Insulin is a hormone produced by the pancreas that makes your body take in glucose (sugar) from the blood. Your body uses glucose to produce energy or stores it for future use. If you have diabetes, your pancreas does not make enough insulin or your body is not able to use properly the insulin it produces. This leads to a high level of glucose in your blood. Metformin helps to lower your blood glucose to a normal level as possible.

Metformin tablets are a medicine used to lower high blood sugar levels in patients with diabetes mellitus (type 2 diabetes); particularly in overweight patients when dietary management and exercise alone does not result in control of blood sugar.

Adults
Your doctor can prescribe Metformin tablets on their own (monotherapy) or in combination with other oral antidiabetic agents, or with insulin.

Children and adolescents
For children from 10 years of age and for adolescents the doctor can prescribe Metformin tablets alone (monotherapy) or in combination with insulin.

2. BEFORE YOU TAKE METFORMIN TABLETS

Do not take Metformin tablets
• if you are **allergic (hypersensitive)** to metformin hydrochloride or any of the other ingredients of Metformin tablets. (Please refer to Section 6 – Further information).

• if you have uncontrolled diabetes, e.g. severe hyperglycaemia (very high levels of glucose in the blood) or ketoacidosis. Ketoacidosis is a state of health, where substances called 'ketone bodies' accumulate in the blood. Symptoms include stomach pain, fast and deep breathing, sleepiness or unusual fruity odour of the breath

• if you have kidney problems.

• if your kidney function worsens as a consequence of e.g.
  • loss of too much water (dehydration) due to long-lasting vomiting or severe diarrhoea. Dehydration may lead to kidney problems, which can put you at risk for lactic acidosis (see ‘take special care with Metformin’ below)

• If you have a severe infection, such as infection affecting your lung or bronchial system or your kidney. Severe infection may lead to kidney problems, which can put you at risk for lactic acidosis. (see ‘take special care with Metformin’ below)

• if you have acute or chronic diseases which may lead to reduced amount of oxygen in body tissues (tissue hypoxia) such as
  • heart failure, or difficulties breathing
  • recent heart attack (myocardial infarction)
  • collapse or trauma (shock)

• if you have liver problems, drink a lot of alcohol or suffer from alcoholism

• if you are breast-feeding.

Make sure you ask your doctor for advice, if:

• you need to have an examination such as X-ray or scan involving the injection of contrast medicines that contain iodine into your bloodstream

• you need to have surgery

You must stop taking Metformin for a certain period of time before and after the examination or the surgery. Your doctor will decide whether you need any other treatment for this time. It is important that you follow your doctor’s instruction precisely.

*Take special care with Metformin tablets*

Normal kidney function is essential for treatment with Metformin tablets because of the risk of developing hyperacidity of the blood. This is due to accumulation of lactic acid (lactic acidosis) and is mainly determined by your kidney function. Symptoms of lactic acidosis are vomiting, bellyache (abdominal pain) with muscle cramps, a general feeling of not being well with severe tiredness, and difficulty in breathing. If this happens to you, you may need immediate treatment. Stop taking Metformin immediately and tell your doctor straight away.

Metformin in itself does not lead to hypoglycaemia (insufficient level of blood sugar), but if you take Metformin with other medicaments for the treatment of diabetes, which can cause hypoglycaemia (e.g. sulphonylureas, insulin) there is a risk of hypoglycaemia. If you experience symptoms of hypoglycaemia such as weakness, dizziness, increased sweating, fast
heart beating, visions disorders or difficulty in concentration, it usually helps to eat or drink something containing sugar.

**Using other medicines**

If you need to have an injection of contrast medicines that contain iodine into your bloodstream, for example for examinations such as X-ray or scan, you must stop taking Metformin for a certain period of time before and after the examination (see 'Make sure you ask your doctor for advice' above).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

During maintenance therapy with Metformin tablets starting or stopping any other medicinal therapy can interfere with your blood sugar control.

Please especially inform your doctor or pharmacist if you are taking or have recently taken any of the following medicines:

- corticosteroids (e.g. prednisone)
- specific medicines for the treatment of high blood pressure (ACE inhibitors, e.g. captopril, enalapril)
- medicines which increase urine production (diuretics, e.g. furosemide)
- specific medicines for the treatment of bronchial asthma (β-agonists, e.g. salbutamol)
- iodinated contrast agents
- medicines containing alcohol.

**Taking Metformin tablets with food and drink**

Drinking alcohol whilst being treated with Metformin tablets increases the possibility of hypoglycaemia (low blood sugar levels) and lactic acidosis. **Therefore**, you should avoid consumption of alcohol while you are taking Metformin.

**Pregnancy and Breast-feeding**

Diabetic women who are pregnant or planning to become pregnant, should not be treated with Metformin tablets. Instead, insulin should be used to maintain blood glucose levels as close to normal as possible. **Inform your doctor if you are pregnant or thinking of becoming pregnant so that he or she can change you to insulin therapy.**

This medicinal product should not be used while breast-feeding (see section “Do not take Metformin tablets” above).

Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**

Taking metformin alone (monotherapy) does not cause low blood sugar levels (hypoglycaemia) and therefore has no effect on your ability to drive or use machines.

Taking metformin in combination with medicines called sulphonylureas, insulin or other treatments for diabetes may cause low blood sugar levels (with symptoms, such as sweating, fainting, dizziness or weakness) and thus affecting your ability to drive and use machines or work safely. **Symptoms of hypoglycemia include weakness, dizziness, increased sweating, fast heart beat, vision disorders or difficulty in concentration. Do not drive or use machines if you start to feel these symptoms.**

3. **HOW TO TAKE METFORMIN TABLETS**

Always take Metformin tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Metformin cannot replace the benefits of a healthy lifestyle. Continue to follow any advice about diet that your doctor has given you and get some regular exercise.

The dose of Metformin tablets should be determined by the doctor according to your blood sugar levels.

Unless prescribed differently by your doctor, the usual dose is:

**Dosage for adults**
The usual starting dose is 500 mg or 850mg metformin hydrochloride Two or three times a day. The maximum daily dose is 3000 mg metformin hydrochloride, taken as 3 divided doses.

**Dosage for children from 10 years of age and adolescents:**
The usual starting dose is 500 mg 850mg metformin hydrochloride once a day. The dosage can be increased up to the maximum recommended daily dose of 2000 mg metformin hydrochloride per day, taken as 2 or 3 divided doses. Treatment of children between 10 and 12 years of age is only recommended on specific advice from your doctor, as experience in this age group is limited.

**Monitoring**
- Your doctor will adapt your dose of Metformin to your blood glucose levels. Make sure that you talk to your doctor regularly. This is particularly important for children and adolescents or if you are an older person.
- Your doctor will also check at least once a year how well your kidneys work. You may need more frequent checks if you are an older person or if your kidneys are not working normally.

**How to take Metformin**
Take the tablets during or after meals with an adequate amount of liquid. Do not chew the tablets. When taking 2 or more tablets you should spread them out over the day, e.g. 1 tablet each during or after breakfast and dinner.
Talk to your doctor if you think the dose of Metformin tablets are too high or too low.

**If you take more Metformin tablets than you should**
Inform your doctor immediately if you have taken more tablets than you should have. An overdose of Metformin tablets does not lead to hypoglycaemia but increases the risk of hyperacidity of the blood caused by lactic acid (lactic acidosis). Symptoms of early hyperacidity are similar to the side effects of metformin on the gastrointestinal tract: sickness, vomiting, diarrhoea and abdominal pain. In severe cases you could also get muscle pain and muscle cramps, very fast breathing which you cannot stop, as well as a clouding of consciousness and coma. This may develop within hours and requires immediate emergency treatment in a hospital.

**If you forget to take Metformin tablets**
If you forget to take Metformin tablets, take the prescribed amount of Metformin tablets at the next prescribed time and try to keep to the prescription in future. Do not take a double dose to make up for a forgotten dose.

**If you stop taking Metformin tablets**
If you stop treatment with Metformin tablets you have to be aware of the risk of uncontrolled blood sugar and of the long-term effects of diabetes mellitus such as damage on eyes, kidneys and blood vessels.
If you have any further questions on the use of this product, ask your doctor or pharmacist.
4. **POSSIBLE SIDE EFFECTS**

Like all medicines, Metformin tablets can cause side effects, although not everybody gets them. Most of the side effects are mild to moderate and will generally disappear after a few days to a few weeks of treatment. Do not be alarmed by this list of possible side effects. You may not experience any of them.

**Other side effects:**
*Very common (affects more than 1 in 10 people)*
- upset stomach, feeling sick (nausea), being sick (vomiting), diarrhoea, stomach ache or loss of appetite. These side effects are most likely to happen at the start of treatment. It helps if you spread the doses over the day and if you take the tablets with or straight after a meal. If symptoms continue, stop taking Metformin and talk to your doctor.

*Common (affects more than 1 in 100 people)*
- taste of metal in your mouth

*Very rare (affects fewer than 1 in 10,000 people)*
- lactic acidosis. This is a very rare but serious complication particularly if your kidneys are not working properly. If you get this complication, you will need immediate treatment. Symptoms of lactic acidosis are vomiting, bellyache (abdominal pain) with muscle cramps, a general feeling of not being well with severe tiredness, and difficulty in breathing. If this happens to you, stop taking Metformin immediately and tell your doctor straight away.
- skin rash (including redness, itching, hives).
- low levels of vitamin B12. Over time this may lead to anaemia, a sore mouth or tongue or possibly numbness or tingling in the limbs.

**The frequencies of the following side effects are not known:**
- abnormalities in liver function tests or hepatitis (inflammation of the liver; this may cause tiredness, loss of appetite, weight loss, with or without yellowing of the skin or whites of the eyes). If this happens to you, stop taking this medicine.

**Children and adolescents**
Limited data in children and adolescents showed that adverse events were similar in nature and severity to those reported in adults.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE METFORMIN TABLETS**

Keep out of the reach and sight of children. If a child is treated with Metformin, parents and caregivers are advised to oversee how this medicine is used.

Do not use Metformin tablets after the expiry date stated on the blister and the carton after “EXP”.

**Storage conditions**
This medicinal product does not require any special storage conditions.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Metformin tablets contain
The active substance is metformin hydrochloride.
Each film coated tablet contains 500 mg, 850 mg or 1000 mg metformin hydrochloride equivalent to 390 mg, 663 mg, and 780 mg of metformin respectively.

The other ingredients are:
Sodium Starch Glycolate (Type A), Povidone K-30, Maize Starch, Colloidal Anhydrous Silica, Magnesium Stearate, Hypromellose 15CP, Talc, Titanium Dioxide (E 171), Macrogol 6000, Propylene Glycol.

What Metformin tablets looks like and contents of the pack
Metformin 500 mg film coated tablets are supplied as white to off white round, biconvex, film coated tablets which are plain on both sides.
Metformin 850 mg film coated tablets are supplied as white to off white capsule shaped, biconvex, film coated tablets which are plain on both sides.
Metformin 1000 mg film coated tablets are supplied as white to off white oval shaped, biconvex, film coated tablets, with a deep breakline on one side and breakline on other side.

Metformin 500 mg, 850 mg and 1000 mg film coated tablets are available in blisters containing 1 (x100), 9, 10, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 180, 200, 300, 500, 600 or 1000 film coated tablets or in plastic bottles containing 10, 20, 21, 30, 40, 50, 56, 60, 90, 100, 120, 180, 200, 300, 400, 500, 600 or 1000 film coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
The marketing authorisation holder is USV Europe Limited, City House, 126-130 Hills Road, Cambridge, CB2 1RY, United Kingdom.

Manufacturers
The manufacturer is Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex HA1 4HF, United Kingdom.

This medicinal product is authorised in the Member States of the EEA under the following names:
Czech Republic Metformin USV Europe 500 mg, 850 mg a 1000 mg potahované tablety
Spain Metformina 850 mg comprimidos recubiertos con película
The Netherlands Metformine HCL USV Europe 500 mg, 850 mg en 1000 mg filmomlaude tabletten
United Kingdom Metformin hydrochloride 500 mg, 850 mg and 1000 mg film coated tablets.

This leaflet was last approved on
Module 4
Labelling

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Metformin hydrochloride 500 mg film-coated tablets

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   
   Each film-coated tablet contains 500 mg, metformin hydrochloride, equivalent to 390 mg metformin.

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**
   
   1 (x100), 9, 10, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 180, 200, 300, 500, 600 or 1000 film coated tablets.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   
   For oral use.
   
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   
   EXP.: 

9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. **NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER**

Marketing Authorisation Holder: USV Europe Limited  
City House, 126 – 130 Hills Road, Cambridge,  
Cambridgeshire CB2 1RY, United Kingdom.

12. **MARKETING AUTHORIZATION NUMBER(S)**

PL 32870/0001

13. **BATCH NUMBER**

BN:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

<-[To be completed nationally]>-

16. **INFORMATION IN BRAILLE**

Metformin hydrochloride 500 mg film-coated tablets

**BLISTER**

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

Blister

1. **NAME OF THE MEDICINAL PRODUCT**

Metformin hydrochloride 500 mg film-coated tablets

2. **NAME OF THE MARKETING AUTHORIZATION HOLDER**

USV Europe Limited

3. **EXPIRY DATE**

EXP:

4. **BATCH NUMBER**

BN:

5. **OTHER**
**PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>**

| Bottle label |

| 1. NAME OF THE MEDICINAL PRODUCT |
| Metformin hydrochloride 500 mg film-coated tablets |

| 2. STATEMENT OF ACTIVE SUBSTANCE(S) |
| Each film-coated tablet contains 500 mg, metformin hydrochloride, equivalent to 390 mg metformin. |

| 3. LIST OF EXCIPIENTS |

| 4. PHARMACEUTICAL FORM AND CONTENTS |
| 10, 20, 21, 30, 40, 50, 56, 60, 90, 100, 120, 180, 200, 300, 400, 500, 600 or 1000 film coated tablets. |

| 5. METHOD AND ROUTE(S) OF ADMINISTRATION |
| For oral use.  
Read the package leaflet before use. |

| 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN |
| Keep out of the reach and sight of children. |

| 7. OTHER SPECIAL WARNING(S), IF NECESSARY |

| 8. EXPIRY DATE |
| EXP.: |

| 9. SPECIAL STORAGE CONDITIONS |

| 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE |
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder: USV Europe Limited.
City House, 126 – 130 Hills Road, Cambridge,
Cambridgeshire CB2 1RY, United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

PL 328700001

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

<To be completed nationally>

16. INFORMATION IN BRAILLE

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<td>Keep out of the reach and sight of children.</td>
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<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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<th>8. EXPIRY DATE</th>
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<tbody>
<tr>
<td>EXP.:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
</tr>
</thead>
</table>
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder: USV Europe Limited.
City House, 126 – 130 Hills Road, Cambridge,
Cambridgeshire CB2 1RY, United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

PL 32870/0002

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

<To be completed nationally>

16. INFORMATION IN BRAILLE

Metformin hydrochloride 850 mg film-coated tablets

BLISTER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Metformin hydrochloride 850 mg film-coated tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

USV Europe Limited

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

BN:

5. OTHER
PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

Bottle Label

1. NAME OF THE MEDICINAL PRODUCT
Metformin hydrochloride 850 mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each film-coated tablet contains 850 mg metformin hydrochloride, equivalent to 663 mg metformin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
10, 20, 21, 30, 40, 50, 56, 60, 90, 100, 120, 180, 200, 300, 400, 500, 600 or 1000 film coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION
For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
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12. MARKETING AUTHORISATION NUMBER(S)

PL 32870/0002

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

-{To be completed nationally}-

16. INFORMATION IN BRAILLE

Metformin hydrochloride 850 mg film-coated tablets
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON &lt;THE OUTER PACKAGING&gt; &lt;AND&gt; &lt;THE IMMEDIATE PACKAGING&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carton</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin hydrochloride 1000 mg film-coated tablets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each film-coated tablet contains 1000 mg of metformin hydrochloride, equivalent to 780 mg metformin.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (x100), 9, 10, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 180, 200, 300, 500, 600 or 1000 film coated tablets.</td>
</tr>
</tbody>
</table>

<table>
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<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
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<tr>
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12. **MARKETING AUTHORISATION NUMBER(S)**

PL 32870/0003

13. **BATCH NUMBER**

BN:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

"[To be completed nationally]"

16. **INFORMATION IN BRAILLE**

Metformin hydrochloride 1000 mg film-coated tablets

**BLISTER**

<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blister</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Metformin hydrochloride 1000 mg film-coated tablets

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

USV Europe Limited

3. **EXPIRY DATE**

EXP.:  

4. **BATCH NUMBER**

BN:

5. **OTHER**
**PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>**

**Bottle Label**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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</thead>
<tbody>
<tr>
<td>Metformin hydrochloride 1000 mg film-coated tablets</td>
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<tr>
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<tr>
<td>Each film-coated tablet contains 1000 mg metformin hydrochloride, equivalent to 780 mg metformin.</td>
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</table>

<table>
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<tr>
<th>3. LIST OF EXCIPIENTS</th>
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</thead>
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<tr>
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<table>
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<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
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</table>

| 10. SPECIAL PRECAUTIONS FOR DISPOSITION OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE |
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Marketing Authorisation Holder: USV Europe Limited.
City House, 126 – 130 Hills Road, Cambridge,
Cambridgeshire CB2 1RY, United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

PL 32870/0003

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

<To be completed nationally>

16. INFORMATION IN BRAILLE

Metformin hydrochloride 1000 mg film-coated tablets
PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

Bottle label

1. NAME OF THE MEDICINAL PRODUCT
Metformin hydrochloride 500 mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each film-coated tablet contains 500 mg, metformin hydrochloride, equivalent to 390 mg metformin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
10, 20, 21, 30, 40, 50, 56, 60, 90, 100, 120, 180, 200, 300, 400, 500, 600 or 1000 film coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION
For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP.: 

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
Marketing Authorisation Holder: USV Europe Limited.
City House, 126 – 130 Hills Road, Cambridge,
Cambridgeshire CB2 1RY, United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)
PL 32870/0014

13. BATCH NUMBER
BN:

14. GENERAL CLASSIFICATION FOR SUPPLY
Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
<[To be completed nationally]> 

16. INFORMATION IN BRAILLE
Metformin hydrochloride 500 mg film-coated tablets
### PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

**Carton**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
<th>Metformin hydrochloride 500 mg film-coated tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. STATEMENT OF ACTIVE SUBSTANCE(S)</td>
<td>Each film-coated tablet contains 500 mg, metformin hydrochloride, equivalent to 390 mg metformin.</td>
</tr>
<tr>
<td>3. LIST OF EXCIPIENTS</td>
<td></td>
</tr>
<tr>
<td>4. PHARMACEUTICAL FORM AND CONTENTS</td>
<td>1 (x100), 9, 10, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 180, 200, 300, 500, 600 or 1000 film coated tablets.</td>
</tr>
<tr>
<td>5. METHOD AND ROUTE(S) OF ADMINISTRATION</td>
<td>For oral use. Read the package leaflet before use.</td>
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<td>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</td>
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<td>BN:</td>
</tr>
<tr>
<td>14. GENERAL CLASSIFICATION FOR SUPPLY</td>
<td>Medicinal product subject to medical prescription.</td>
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<tr>
<td>15. INSTRUCTIONS ON USE</td>
<td>&lt;[To be completed nationally]&gt;</td>
</tr>
<tr>
<td>16. INFORMATION IN BRAILLE</td>
<td>Metformin hydrochloride 500 mg film-coated tablets</td>
</tr>
<tr>
<td><strong>PARTICULARS TO APPEAR ON &lt;THE OUTER PACKAGING&gt; &lt;AND&gt; &lt;THE IMMEDIATE PACKAGING&gt;</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Bottle Label</strong></td>
<td></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**  
Metformin hydrochloride 850 mg film-coated tablets

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**  
Each film-coated tablet contains 850 mg metformin hydrochloride, equivalent to 663 mg metformin.

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**  
10, 20, 21, 30, 40, 50, 56, 60, 90, 100, 120, 180, 200, 300, 400, 500, 600 or 1000 film coated tablets.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**  
For oral use.  
Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**  
Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**  
EXP.: 

9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**  
Marketing Authorisation Holder: USV Europe Limited.  
City House, 126 – 130 Hills Road, Cambridge, Cambridgeshire CB2 1RY, United Kingdom.

12. **MARKETING AUTHORISATION NUMBER(S)**  
PL 32870/0015

13. **BATCH NUMBER**  
BN:

14. **GENERAL CLASSIFICATION FOR SUPPLY**  
Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**  
< [To be completed nationally] >

16. **INFORMATION IN BRAILLE**  
Metformin hydrochloride 850 mg film-coated tablets
PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

1. NAME OF THE MEDICINAL PRODUCT
   Metformin hydrochloride 850 mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)
   Each film-coated tablet contains 850 mg metformin hydrochloride, equivalent to 663 mg metformin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
   1 (x100), 9, 10, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 180, 200, 300, 500, 600 or 1000 film coated tablets

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    PL 32870/0015

13. BATCH NUMBER
    BN:

14. GENERAL CLASSIFICATION FOR SUPPLY
    Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
    <[To be completed nationally]>

16. INFORMATION IN BRAILLE
    Metformin hydrochloride 850 mg film-coated tablets
**1. NAME OF THE MEDICINAL PRODUCT**
Metformin hydrochloride 1000 mg film-coated tablets

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**
Each film-coated tablet contains 1000 mg metformin hydrochloride, equivalent to 780 mg metformin.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**
10, 20, 21, 30, 40, 50, 56, 60, 90, 100, 120, 180, 200, 300, 400, 500, 600 or 1000 film coated tablets.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**
For oral use.
Read the package leaflet before use.

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**14. GENERAL CLASSIFICATION FOR SUPPLY**
Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**
<[To be completed nationally]>

**16. INFORMATION IN BRAILLE**
Metformin hydrochloride 1000 mg film-coated tablets
PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

Carton

1. NAME OF THE MEDICINAL PRODUCT
Metformin hydrochloride 1000 mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each film-coated tablet contains 1000 mg metformin hydrochloride, equivalent to 780 mg metformin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
1 (x100), 9, 10, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 180, 200, 300, 500, 600 or 1000 film coated tablets

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Keep out of the reach and sight of children.

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13. BATCH NUMBER
BN: 

14. GENERAL CLASSIFICATION FOR SUPPLY
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15. INSTRUCTIONS ON USE
<[To be completed nationally]>

16. INFORMATION IN BRAILLE
Metformin hydrochloride 1000 mg film-coated tablets
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for Metformin Hydrochloride 500, 850 and 1000mg Film-coated Tablets (PL 32870/0001-3; UK/H/1962 and 2397/001-3/DC) could be approved. The products are prescription-only medicines for the treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83 EC, as amended, claiming to be generic medicinal products of Glucophage 500, 850 and 1000mg, which were originally granted in to Merck BV in Belgium in 1962.

Metformin hydrochloride is a biguanide used in the treatment of diabetes mellitus, because of its glucose-lowering properties. It acts by inhibiting hepatic glucose production and also gluconeogenesis and glycogenolysis. Metformin increases insulin sensitivity in muscles, as well as improving peripheral glucose uptake and utilisation. In addition, it delays intestinal glucose absorption. It does not stimulate insulin secretion.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Metformin Hydrochloride 500mg Film-Coated Tablets  
                          Metformin Hydrochloride 850mg Film-Coated Tablets  
                          Metformin Hydrochloride 1000mg Film-Coated Tablets |
| Name(s) of the active substance(s) (INN) | Metformin hydrochloride |
| Pharmacotherapeutic classification (ATC code) | Biguanides  
                          (A10 BA02) |
| Pharmaceutical form and strength(s) | 500mg, 850mg and 1000mg Film-Coated Tablets |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1962 and 2397/001-3/DC |
| Reference Member State | United Kingdom |
| Member States concerned | UK/H/1962/001-3/DC – Belgium, Czech Republic, Denmark, Finland, Germany, Netherlands, Norway, Poland, Slovak Republic, Spain and Sweden  
                          UK/H/2397/001-3/DC – Czech Republic, Netherlands and Spain |
| Marketing Authorisation Number(s) | PL 32870/0001-3 and 0014-6 |
| Name and address of the authorisation holder | USV Europe Limited, City House, 126 – 130 Hills Road, Cambridge, Cambridgeshire CB2 1RY, United Kingdom |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Active substance

INN:       Metformin hydrochloride
Chemical Name:  Imidodicarboximimidic diamide, N, N-dimethyl-, monohydrochloride
               1,1-Dimethylbiguanide monohydrochloride
Molecular Formula:  C₄H₁₁N₅.HCl
Chemical Structure:

![Chemical Structure](image)

Molecular Weight:  165.62
Appearance:       A white crystalline substance, freely soluble in water, slightly soluble in alcohol, and practically insoluble in acetone and methylene chloride. It exhibits no polymorphism.

Metformin hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance metformin hydrochloride are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

P.  Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients sodium starch glycolate (Type A), povidone K-30, maize starch, colloidal anhydrous silica, magnesium stearate, hypromellose 15cP, talc, titanium dioxide (E 171), macrogol 6000 and propylene glycol.

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

None of the excipients is sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate stable, efficacious and tolerable film-coated tablets containing metformin hydrochloride that can be considered generic medicinal products of Glucophage 500, 850 and 1000mg Tablets (Merck BV).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products.
Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed for all strengths are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
All strengths of tablets are packaged in transparent polyvinylchloride/aluminium blisters or high density polyethylene (HDPE) containers and closures with foil seal induction. The pack sizes for the blisters are 1 (x100), 9, 10, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 180, 200, 300, 500, 600 or 1000 film coated tablets. The pack sizes for the HDPE containers are 10, 20, 21, 30, 40, 50, 56, 60, 90, 100, 120, 180, 200, 300, 400, 500, 600 or 1000 film coated tablets.

Not all pack sizes are to be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with no specific storage conditions.

Suitable post approval stability commitments have been provided to follow-up the batches from the current studies.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
A suitable justification has been provided for not submitting a risk management plan for these products.

**MAA forms**
The MAA forms are pharmaceutically satisfactory.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
The grant of marketing authorisations is recommended.

**III.2 PRE-CLINICAL ASPECTS**
As the pharmacodynamic, pharmacokinetic and toxicological properties of metformin hydrochloride are well-known, no further studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

**III.3 CLINICAL ASPECTS**

**Pharmacokinetics**
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence studies:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Metformin Hydrochloride 500mg Film-coated Tablets versus the reference product Glucophage 500mg (Merck BV, The Netherlands) in healthy male volunteers under fasted conditions.

Volunteers were dosed with either treatment, given with 50g of glucose dissolved in 200ml of water, after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 36 hours post dose. The two treatment arms were separated by a 7-day washout period.

The results are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>% Ratio T/R</th>
<th>90% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>1187.13</td>
<td>1200.15</td>
<td>98.91</td>
<td>92.35-105.95</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>6961.72</td>
<td>7007.78</td>
<td>99.34</td>
<td>92.44-106.76</td>
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<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt;</td>
<td>7482.44</td>
<td>7498.04</td>
<td>99.79</td>
<td>92.92-107.17</td>
</tr>
</tbody>
</table>

* for the log-transformed data

The test and reference products are within conventional 90% CI limits of 80-125% for metformin. In conclusion, bioequivalence has been shown between the test and reference products.
An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Metformin Hydrochloride 1000mg Film-coated Tablets versus the reference product Glucophage 1000mg (Merck BV, The Netherlands) in healthy male volunteers under fasted conditions.

Volunteers were dosed with either treatment, given with 50g of glucose dissolved in 200ml of water, after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 36 hours post dose. The two treatment arms were separated by a 7-day washout period.

The results are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>% Ratio T/R</th>
<th>90% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>2448.23</td>
<td>2660.46</td>
<td>92.02</td>
<td>87.41-96.88</td>
</tr>
<tr>
<td>AUC0-t</td>
<td>14032.33</td>
<td>15100.54</td>
<td>92.93</td>
<td>89.45-96.54</td>
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<tr>
<td>AUC0-inf</td>
<td>14887.36</td>
<td>15875.90</td>
<td>93.77</td>
<td>90.43-97.24</td>
</tr>
</tbody>
</table>

The test and reference products are within conventional 90% CI limits of 80-125% for metformin. In conclusion, bioequivalence has been shown between the test and reference products.

As the 850mg and 1000mg products meet all the criteria as specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 1000mg strength can be extrapolated to the 850mg strength tablets also.

**Efficacy**
No new data on the efficacy have been submitted and none are required for these types of applications.

**Safety**
No new or unexpected safety issues were raised by the bioequivalence data.

**SPC, PIL, Labels**
The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

**Clinical Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Conclusion**
The grant of marketing authorisations is recommended.
IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Metformin Hydrochloride 500, 850 and 1000mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Metformin Hydrochloride 500 and 1000mg Film-coated Tablets and their respective reference products. As the 850mg and 1000mg products meet all the criteria as specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 1000mg strength can be extrapolated to the 850mg strength tablets also.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory and consistent with those for the reference products Glucophage 500, 850 and 1000mg (Merck BV).

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence studies supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with metformin hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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