SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Abiano 1000 mg Effervescent tablets

Metformin hydrochloride 1000mg effervescent tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 1000 mg metformin hydrochloride corresponding to 780 mg metformin.

Excipient(s) with known effect:

Sodium. This medicinal product contains 94.14 mg sodium per effervescent tablet.

Isomalt. This medicinal product contains 370 mg isomalt per effervescent tablet.

Sucrose. This medicinal product contains 2.09 mg sucrose per effervescent tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablets

White, round, flat-faced, bevel-edged, bisect, effervescent tablets with an average diameter 23 mm. The effervescent tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- In adults, metformin may be used as monotherapy or in combination with other oral anti- diabetic agents or with insulin.
- In children from 10 years of age and adolescents, metformin may be used as monotherapy or in combination with insulin.

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

4.2 Posology and method of administration

Posology

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.

The maximum recommended dose of metformin hydrochloride is 3000 mg daily, taken as 3 divided doses.

If transfer from another oral antidiabetic agent is intended: the other agent should be discontinued and metformin hydrochloride may be initiated 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 metformin hydrochloride 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 hydrochloride dosage should be adjusted based on renal function and regular assessment of renal function is also necessary (see section 4.4).

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

GFR ml/min	The total maximum daily dose (divided in 1, 2 or 3 doses)	Additional considerations
60-89	3000 mg	Dose reduction may be considered in relation to declining renal function.
45-59	2000 mg	Factors that may increase

30-44	1000 mg	the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.
<30	-	Metformin is contraindicated.

Paediatric population

Monotherapy and combination with insulin

Metformin 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.

The posology described in section 4.2 cannot always be achieved with this product, yet such doses can be achieved with other available drug products.

Method of administration

The effervescent tablets can be divided into two equal doses. The remaining part of the effervescent tablet if not used immediately, should be discarded. The effervescent tablets must be dissolved in a glass of water and the solution should then be drunk immediately after complete dissolution of the tablets.

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients listed in section 6.1.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma.
- Severe renal failure (GFR <30 ml/min)
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.

- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.

4.4 Special warnings and precautions for use

Lactic acidosis
Lactic acidosis is a very rare, but serious (high mortality rate 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 impaired renal failure, or acute worsening of renal function. Special caution should be paid to situations where renal function may become impaired, for example in case of dehydration (severe diarrhoea or vomiting), or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). In the acute conditions listed, metformin hydrochloride should be temporarily discontinued.

Other associated risk factors should be considered to avoid lactic acidosis such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia (such as: decompensated cardiac failure, acute myocardial infarction) (see also section 4.3 and section 4.5).

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5mmol/l, and an increased anion gap and lactate/pyruvate ratio. In case of lactic acidosis, the patient should be hospitalised immediately (see section 4.9).

Physicians should alert the patients and/or care-givers on the risk and on the symptoms of lactic acidosis.

Patients with known or suspected mitochondrial diseases:

In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Renal function

eGFR should be determined before initiating treatment and regularly thereafter:
at least annually in patients with normal renal function,
at least two to four times a year in patients with creatinine clearance levels at the lower limit of normal and in elderly subjects.
In case (eGFR < 30 ml/min/1.73 m^2), metformin hydrochloride is contraindicated (see section 4.2) and should be temporarily discontinued in the presence of conditions that alter renal function, see section 4.3.

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

Cardiac function
Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin hydrochloride may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, metformin hydrochloride is contraindicated (see section 4.3).

Administration of iodinated contrast media
The intravascular administration of iodinated contrast agents can lead to contrast induced nephropathy. This may induce metformin accumulation and may increase the risk for lactic acidosis. Metformin hydrochloride must be discontinued prior to, or at the time of the test and not be reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.5.

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

Paediatric population
The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin hydrochloride is initiated.
No effect of metformin hydrochloride on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin hydrochloride on these parameters in metformin hydrochloride-treated children, especially pre-pubescent children, is recommended.

Children aged between 10 and 12 years
Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of metformin hydrochloride in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

Other precautions
All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
The usual laboratory tests for diabetes monitoring should be performed regularly.
Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.
Metformin hydrochloride alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

This medicine contains sodium

This medicinal product contains 94.14 mg sodium per effervescent tablet, equivalent to 4.7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicine contains isomalt
This medicinal product contains 370 mg isomalt per effervescent tablet. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
This medicine contains sucrose
This medicinal product contains 2.09 mg sucrose per effervescent tablet. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. Also, this medicine may be harmful to the teeth.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

- ***Alcohol***

Acute alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic insufficiency.

- *Iodinated contrast media*

Metformin hydrochloride must be discontinued prior to the time of the test and not be reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further (see section 4.4).

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

- *Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics)*

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, the metformin dosage should be adjusted during the therapy with the respective medicinal products and upon its discontinuation.

- *Diuretics especially loop diuretics*

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

- *Organic cation transporters (OCT)*

Metformin is a substrate of both transporters OCT1 and OCT2.

Coadministration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are coadministered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.

A limited amount of data from the use of metformin hydrochloride in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development (see section 5.3).

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin, but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus.

Breast-feeding

Metformin hydrochloride is excreted into human breast milk. No adverse effects were observed in breastfed newborns / infants. However, as only limited data are available, breast-feeding is not recommended during metformin hydrochloride treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breast-feeding and the potential risk to adverse effects on the child.

Fertility

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

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

The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows: very common: $\geq$1/10; common $\geq$1/100, <1/10; uncommon $\geq$1/1,000, <1/100; rare $\geq$1/10,000, <1/1,000; very rare <1/10,000.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders

Common:

- Vitamin B12 decrease/deficiency (see section 4.4).

Very rare:

- Lactic acidosis (see section 4.4).

Nervous system disorders

Common:

- Taste disturbance

Gastrointestinal disorders

Very common:

- Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders

Very rare:

- Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders

Very rare:

- Skin reactions such as erythema, pruritus, urticarial.

Paediatric population

In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 the hospital. The most effective method to remove lactate and metformin hydrochloride is haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization
- delay of intestinal glucose absorption.

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

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

Pharmacodynamic effects

In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

In humans, independently of its action on glycaemia, metformin 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 study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes.

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

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin hydrochloride group (29.8 events/ 1000 patient-years) versus diet alone (43.3 events/ 1000 patient-years), p= 0.0023, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/ 1000 patient-years), p= 0.0034;

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

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

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

Paediatric population

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

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

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

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

Distribution

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

Biotransformation

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

Elimination

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

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

Characteristics in specific groups of patients

Pediatric population

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

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC_{0-t}) were reduced by approximately 33 % and 40 %, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone (PVP K-30) (E1201)

Sodium Hydrogen Carbonate (E500)

Sodium Carbonate (E500)

Lemon Flavour in Powder (containing: natural flavouring substances in concentration 20.0 %, maltodextrin (maize) in concentration 65.5 %, modified starch E1450 (waxy maize) in concentration 5.0 %, sugar (sucrose) in concentration 9.5 %)

Citric Acid Crystalline (E330)

Citric Acid Powder (E330)

Potassium Acesulfame (E950)

Isomalt (E953)

Sodium Cyclamate (E952)

Glycine (E 640)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

In case of splitting of the effervescent tablet, the remaining part if not used immediately should be discarded.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Each cardboard box contains 28, 30 or 90 effervescent tablets presented in Al/PE strips, along with a Patient Information Leaflet.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Aspire Pharma Limited
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Bedford Road,
Petersfield,
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GU32 3QG

8 MARKETING AUTHORISATION NUMBER(S)

PL 35533/0292

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/01/2021

10 DATE OF REVISION OF THE TEXT

10/04/2025