SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Brotmin 500 mg film-coated tablets
Brotmin 850 mg film-coated tablets
Brotmin 1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.
Each film-coated tablet contains 850 mg metformin hydrochloride corresponding to 662.9 mg metformin base.
Each film-coated tablet contains 1000 mg metformin hydrochloride corresponding to 780 mg metformin base.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Brotmin 500 mg film coated tablets: White oval film-coated tablets, plain on both sides, with dimensions 16mm x 8mm
Brotmin 850 mg film coated tablets: Yellow oval film-coated tablets, embossed 'MC' on one side and plain on the other side, with dimensions 20.1mm x 9.8mm.
Brotmin 1000 mg film coated tablets: White oval film-coated tablets, with a score line on both sides, with dimensions 21.2mm x10.2mm. The 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 glycaemic control.

In adults, metformin may be used as monotherapy or in combination with other oral antidiabetic agents or with insulin.

In children from 10 years of age and adolescents, metformin may be used as monotherapy or in combination with insulin.

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

4.2 Posology and method of administration

Posology
Adults with normal renal function (GFR ≥90 mL/min)
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 hydrochloride dose (2 to 3 grams per day), it is possible to replace two Brotmin 500 mg film-coated tablets with one Brotmin 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 at the dose indicated above.

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

Elderly
Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is 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)	*Total maximum daily dose (to be divided into 2-3 daily 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 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.
30-44	1000 mg	
<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 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.

Method of administration
Oral administration.
Precautions to be taken before handling or administering the medicinal product.

4.3 Contraindications

Hypersensitivity to the active substance(s) 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 <30mL/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, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.
In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.
Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).
Patients and/or care-givers should be informed of the risk of lactic acidosis. 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 (<7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

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
GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR <30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section 4.3.

Cardiac function
Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function.
For patients with acute and unstable heart failure, metformin is contraindicated (see section 4.3).

Administration of iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.5.

Surgery
Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Paediatric population

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

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

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

The usual laboratory tests for diabetes monitoring should be performed regularly.

Metformin 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 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 less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended
Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Iodinated contrast agents
Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 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, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2.
Co-administration 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 co-administered 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 hyperglycaemia in the periconceptional phase and during pregnancy is associated with increased risk of congenital abnormalities, pregnancy loss, pregnancy-induced hypertension, preeclampsia, and perinatal mortality. It is important to maintain blood glucose levels as close to normal as possible throughout pregnancy, to reduce the risk of adverse hyperglycaemia-related outcomes to the mother and her child.
Metformin crosses the placenta with levels that can be as high as maternal concentrations.
A large amount of data on pregnant women (more than 1000 exposed outcomes) from a register-based cohort study and published data (meta-analyses, clinical studies, and registries) indicates no increased risk of congenital abnormalities nor feto/neonatal toxicity after exposure to metformin in the periconceptional phase and/or during pregnancy.
There is limited and inconclusive evidence on the metformin effect on the long-term weight outcome of children exposed in utero. Metformin does not appear to affect motor and social development up to 4 years of age in children exposed during pregnancy although data on long term outcomes are limited.
If clinically needed, the use of metformin can be considered during pregnancy and in the periconceptional phase as an addition or an alternative to insulin.

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

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

4.7 Effects on ability to drive and use machines

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines. However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulfonylureas, insulin or meglitinides).

4.8 Undesirable effects

During treatment initiation, the most common adverse reactions are nausea, vomitting, 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, 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, urticaria.

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

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 the national reporting system.
ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Metformin is a biguanide with antihyperglycaemic effects, on both basal and postprandial hyperglycaemia. It does not stimulate insulin secretion and therefore does not cause hypoglycaemia.

Metformin reduces basal hyperinsulinemia, and in combination with insulin, reduces insulin requirement.

Metformin exerts its antihyperglycaemic effect via multiple mechanisms:
Metformin reduces hepatic glucose production.
Metformin facilitates peripheral glucose uptake and utilization, in part by increasing insulin action.

Metformin alters glucose turnover in the gut: Uptake from circulation is increased and absorption from food is decreased. Additional mechanisms attributed to the gut include an increase in release of glucagon-like peptide 1 (GLP-1) and a decrease of bile acid resorption. Metformin alters the gut microbiome.

Metformin can improve the lipid profile in hyperlipidaemic individuals.

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

Metformin is an adenosine monophosphate-protein-kinase (AMPK) activator and increases the transport capacity of all types of membrane glucose transporters (GLUTs).

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

Benefit regarding clinical outcome has not been shown for metformin used as second-line therapy, in combination with a sulfonylurea.
In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

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 (Cmax) is reached in approximately 2.5 hours (tmax). Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.
After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.
At the recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 5 µg/ml, even at maximum doses.
Food decreases the extent and slightly delays the absorption of metformin. Following oral administration of a 850 mg tablet, a 40% lower 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 partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution.
The mean volume of distribution (Vd) ranged between 63-276 l.

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

Elimination
Renal clearance of metformin is >400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.
When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Characteristics in specific groups of patients
Renal impairment
The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations (see section 4.2).

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

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily 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 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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Croscarmellose sodium
Povidone K 30
Cellulose, Microcrystalline
Magnesium stearate

Film coat:
500 mg and 1000 mg:
Poly(vinyl alcohol)
Titanium dioxide (E171)
Macrogols
Talc

850 mg:
Iron oxide yellow (E172)
Poly(vinyl alcohol)
Titanium dioxide (E171)
Macrogols
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

500 mg tablets:
9, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 200, 500, 600 or 1000 tablets in blister packs (PVC-aluminium)

Not all pack sizes may be marketed.

850 mg and 1000 mg tablets:
8, 9, 10, 14, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 300, 600 or 1000 tablets in blister packs (PVC-aluminium)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Medochemie Ltd,

1-10 Konstantinoupoleos Street, 3011 Limassol

Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

MA032/14201
MA032/14202
MA032/14203

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st April 2021
Date of latest renewal: 10th July 2025

10. DATE OF REVISION OF THE TEXT

02/2026