Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1.3 Product Information

1.3.1 SPC, Labeling and Package Leaflet

SPC-Summary of Product Characteristics

Name of the proprietary product: Metcare 850

Name of the nonproprietary International Product: Metformin hydrochloride BP Tablets 850 mg

Route of Administration: Oral Tablets

2. Qualitative and Quantitative composition:

Each uncoated tablet contains:

Metformin HCL 850 mg

Excipients…..... Q.S.

Batch size: 100000 Tablets

3. PHARMACEUTICAL FORM

Uncoated Tablet.

White coloured caplet shaped biconvex uncoated tablet having break line on one side of each tablets.

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 850mg 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 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 as first-line therapy after diet failure

4.2 Posology and method of administration

Route: Oral

Adults:

Adults with normal renal function (GFR≥ 90 mL/min)

Monotherapy and combination with other oral antidiabetic agents:

- The usual starting dose is one tablet 2 or 3 times daily given during or after meals. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability.

The maximum recommended dose of metformin is 3g daily, taken as 3 divided doses.

- If transfer from another oral anti-diabetic is intended, discontinue the other agent and initiate metformin at the dose indicated above.

Combination with insulin:

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

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	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

Elderly: Due to 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 tablets can be used in children from 10 years of age and adolescents.

• The usual starting dose is one tablet of 850 mg or 850 mg 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 is 2 g daily, taken as 2 or 3 divided doses.

4.3 Contraindications

• Hypersensitivity to metformin hydrochloride or to any of the Excipients listed in section 6.1.

• diabetic pre-coma

• 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:

- respiratory failure

- decompensated heart failure

- recent myocardial infarction

- shock

• Hepatic insufficiency, acute alcohol intoxication, alcoholism

• Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)

• Severe renal failure (GFR <30 mL/min)

4.4 Warning and Precaution

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 inadequately controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see section 4.3 and 4.5)

Patients and/or care-givers should be informed of the risk of lactic acidosis.

Diagnosis:

Lactic acidosis is characterised by acidotic dysponea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patients 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 (see section 4.9).

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.

As metformin is excreted by the kidneys, 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

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

Administration of iodinated contrast agent:

As the intravenous administration of iodinated contrast material in radiologic studies can 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 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 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 on these specific points are available.

Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially pre-pubescent children, is recommended

Children aged between 10 to 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 efficacy and safety in this group of children 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 alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

4.5Interaction 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.

Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast agents (see section 4.4)

Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours, 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 cyclooxygenase (COX) II inhibitors, ACE inhibitors, angiotension II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combinations with metformin, close monitoring of renal function is necessary.

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 the 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.

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 Pregnancy and lactation

Pregnancy

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

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

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

Breast-feeding

Metformin 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 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 (sulfonylureas, insulin, repaglinide)

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 undesirable effects may occur under treatment with metformin hydrochloride. Frequencies are defined as follows: very common: 1/10; common>1/100, <1/10; uncommon>1/1,000, <1/100; rare>1/10,000, <1/1,000; very rare<1/10,000, not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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: Lactic acidosis (see section 4.4).

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 present with megaloblastic anaemia.

Hepatobiliary disorders:

Very rare: Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin hydrochloride discontinuation.

4.9 Overdose

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

remove lactate and metformin is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Biguanide oral hypoglycaemic agents

ATC Code: A10BA02

Mechanism of action

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and post-prandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

1. Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.

2. In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation.

3. And delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (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 has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: Metformin reduces total cholesterol, LDL, cholesterol and triglycerides levels.

Clinical Efficacy:

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

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

• A significant reduction of the absolute risk of any diabetes-related complications in metformin group (29.8 events/1000 patients-years) versus diet alone (43.3 events/1000 patient-years), p= 0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1000 patients-years), p=0.0034.

• A significant reduction of the absolute risk of the diabetes-related mortality: Metformin hydrochloride 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-year, 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 sulphonylurea 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 patients-years, diet alone 18 events/1000 patients-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 I 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, Tmax is reached in 2.5 hours. Absolute bioavailability of a 850mg or 850mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and the dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1μg/ml. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 4μg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin hydrochloride.

Following administration of a dose of 850mg, 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 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.

Metabolism

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

Elimination:

Renal clearance of metformin is >400ml/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 850 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 850 mg twice 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 850 mg twice 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 reveals no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1	Maize Starch	BP
2	Microcrystalline Cellulose	BP
3	Povidone	BP

4	Purified Water	BP
5	Sodium Methylparaben	BP
6	Sodium Propylparaben	BP
7	Purified Talc	BP
8	Magnesium Stearate	BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years from the date of manufacture.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original packaging to protect from moisture

6.5 Nature and contents of container

Blister pack of 10 tablets. Such 10 blister is packed in printed carton along with one leaflet

6.6 Special precautions for disposal and other Special handling

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

7. REGISTRANT

Merit Organics Ltd

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Dist- Valsad-396155, Gujarat , INDIA

8. MANUFACTURER

Merit Organics Ltd

Plot No 2104/2/A, G.I.D.C , Sarigam , Bhilad,

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9. DATE OF REVISION OF THE TEXT

Applicable once the registration is obtained.