Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Yaltormin SR 750mg Prolonged Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged release tablet contains 750 mg metformin hydrochloride corresponding to 585 mg metformin base.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged Release Tablets

White to off-white, capsule shaped tablet debossed with ‘SR 750’ on one side and plain on other side. The tablets are approximately 19.6 mm in length and 9.3 mm in breadth.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Yaltormin SR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

4.2 Posology and method of administration

Posology

Monotherapy and combination with other oral antidiabetic agents:
Yaltormin SR 750 mg is intended for patients who are already treated with metformin tablets (prolonged or immediate release).

The dose of Yaltormin SR 750 mg should be equivalent to the daily dose of metformin tablets (prolonged or immediate release), up to a maximum dose of 1500 mg given with the evening meal.

After 10 to 15 days, it is recommended to check that the dose of Yaltormin SR 750 mg is adequate on the basis of blood glucose measurements.

Combination with insulin:
For patients already treated with metformin and insulin in combination therapy, the dose of Yaltormin SR 750 mg should be equivalent to the daily dose of metformin tablets up to a maximum of 1500 mg given with the evening meal, 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).

Patients with renal impairment:
Metformin may be used in patients with moderate renal impairment, stage 3a (creatinine clearance [CrCl] 45 – 59 ml/min or estimated glomerular filtration rate [eGFR] 45-59 ml/min/1.73m^2) only in the absence of other conditions that may increase the risk of lactic acidosis and with the following dose adjustments:

- the starting dose is 500 mg or 750 mg metformin hydrochloride, once daily. The maximum dose is 1000 mg daily (see section 5.2). The renal function should be closely monitored (every 3-6 months).

If CrCl or eGFR fall < 45 ml/min or < 45 ml/min/1.73m^2 respectively, metformin must be discontinued immediately.

Paediatric population:
In the absence of available data, Yaltormin SR should not be used in children.

Method of administration

The tablets should be swallowed whole with a drink of water. They should not be chewed or crushed.

4.3 Contraindications

- Hypersensitivity to metformin or to any of the excipients listed in section 6.1
- Diabetic ketoacidosis, diabetic pre-coma
- Moderate (stage 3b) and severe renal failure or renal dysfunction (CrCL < 45 ml/min or eGFR < 45 mL/min/1.73m^2)
- 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 accumulation. Reported cases of lactic acidosis in patients on metformin 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 diarrhea 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 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).

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps, digestive disorders as abdominal pain and severe asthenia. Patients should be instructed to notify these signs immediately to their physicians if they occur, notably if patients had a good tolerance to metformin before. Metformin should be discontinued, at least temporarily, until the situation is clarified. Reintroduction of metformin should then be discussed taking into account the benefit/risk ratio in an individual basis as well as renal function.

Diagnosis:
Lactic acidosis is characterized by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an

increased anion gap and lactate/pyruvate ratio. In case of lactic acidosis, the patient should be hospitalised immediately (see section 4.9).

Physicians should alert the patients on the risk and on the symptoms of lactic acidosis.

Renal function:
As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels by using the Cockcroft-Gault formula) or 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 creatinine clearance CrCl is <45 ml/min (eGFR < 45 ml/min/1.73 m^2), metformin is contraindicated (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 in case of dehydration, or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).

In these cases, it is also recommended to check renal function before initiating treatment with metformin.

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 media:
The intravascular administration of iodinated contrast media in radiological studies can lead to renal failure. This may induce metformin accumulation and may increase the risk for lactic acidosis. In patients with eGFR > 60mL/min/1.73m^2, metformin must be discontinued prior to, or at the time of the test and not reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further (see section 4.5).

In patients with moderate renal impairment (eGFR between 45 and 60 ml/min/1.73 m^2), metformin must be discontinued 48 hours before administration of iodinated contrast media 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 4.5).

Surgery:
Metformin should be discontinued 48 hours before elective surgery with 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.

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. sulphonylureas or meglitinides).

The tablet shells may be present in the faeces. Patients should be advised that this is normal.

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 in acute alcohol intoxication, particularly in case of:
- fasting or malnutrition,
- hepatic insufficiency.

Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast media
Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and an increased risk of lactic acidosis.

In patients with eGFR > 60mL/min/1.73m^2, metformin must be discontinued prior to, or at the time of the test and not 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).

In patients with moderate renal impairment (eGFR between 45 and 60 ml/min/1.73 m^2), metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.

Combinations requiring precautions for use

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 other drug and upon its discontinuation.

Diuretics, especially loop diuretics
They may increase the risk of lactic acidosis due to their potential to decrease renal function.

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 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 fetal 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 is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding 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 effect 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. sulphonylureas, insulin, or meglinitides).

4.8 Undesirable effects

In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with metformin SR was similar in nature and severity to that reported in patients treated with metformin immediate release.

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

The following adverse reactions may occur with Yaltormin SR.

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.

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

Metabolism and nutrition disorders
Very rare:

- Lactic acidosis (see 4.4. Special warnings and precautions for use).
- Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia.

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. 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

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ORAL ANTI-DIABETICS
(A10BA02: Gastrointestinal tract and metabolism)

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

Mechanism of action

Metformin 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 utilisation
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

Pharmacodynamic effects

In clinical studies, the major non glycemic effect of metformin is either weight stability or modest weight loss.

In humans, independently of its action on glycaemia, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

Clinical efficacy

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in overweight type 2 diabetic patients treated with immediate release metformin as first-line therapy after diet failure. 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 sulphonylurea 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 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 11 events/ 1000 patient-years, diet alone 18 events/ 1000 patient-years (p=0.01)

For metformin used as second-line therapy, in combination with a sulphonylurea, benefit regarding clinical outcome has not been shown.

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

5.2 Pharmacokinetic properties

Absorption
Following a single oral administration of 1500 mg of metformin SR 750 mg, a mean peak plasma concentration of 1193 ng/ml is achieved with a median value of 5 hours and a range of 4 to 12 hours.

Metformin SR 750 mg was shown to be bioequivalent to metformin SR 500 mg at a 1500 mg dose with respect to Cmax and AUC in healthy fed and fasted subjects.

The bioequivalent product shows the following properties:
At steady state, similar to the immediate release formulation, Cmax and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000mg of metformin prolonged release tablets is similar to that observed after administration of 1000mg of metformin immediate release tablets b.i.d.
Intrasubject variability of Cmax and AUC of metformin prolonged release tablets is comparable to that observed with metformin immediate release tablets.
When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both Cmax and Tmax are unaffected).
Metformin absorption from the prolonged release formulation is not altered by meal composition.
No accumulation is observed after repeated administration of up to 2000mg of metformin prolonged release tablets.

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.

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

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

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).

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Silica colloidal anhydrous
Carmellose sodium
Hypromellose

6.2 Incompatibilities

None

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

28 and 56 tablets in blister strips composed of aluminium foil and PVC.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
Ash Road North
Wrexham
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1339/063/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th April 2016

10 DATE OF REVISION OF THE TEXT

June 2016