SUMMARY OF PRODUCT CHARACTERISTICS

1   NAME OF THE MEDICINAL PRODUCT

Metformin hydrochloride 750mg Prolonged-release Tablets

2   QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3   PHARMACEUTICAL FORM

Prolonged-release tablet.

Metformin hydrochloride750mg Prolonged-release Tablets are white to off-white, capsule shaped, uncoated tablets, 19.60 mm in length, 9.30 mm in width and 7.40 mm in thickness, debossed with 'XR 750' on one side and plain on other side

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. Metformin prolonged-release tablets may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

4.2   Posology and method of administration

Posology

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

Monotherapy and combination with other oral anti-diabetic agents
The usual starting dose is one Metformin 500mg Prolonged-release Tablet once daily.

After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 4 tablets of Metformin hydrochloride 500mg Prolonged-release Tablets daily.

Dosage increases should be made in increments of 500mg every 10-15 days, up to a maximum of 2000mg once daily with the evening meal. If glycaemic control is not achieved on 2000mg once daily, 1000mg twice daily should be considered, with both doses being given with food, at the time of the morning and evening meals. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000mg daily.

In patients already treated with metformin tablets, the starting dose of Metformin hydrochloride Prolonged-release Tablets should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin at a dose above 2000mg daily, switching to Metformin hydrochloride Prolonged-release Tablets is not recommended.

Metformin hydrochloride 750mg and 1000mg Prolonged-release Tablets are intended as maintenance therapy for patients currently treated with metformin tablets (prolonged or immediate release).

The dose of Metformin hydrochloride 750mg or 1000mg Prolonged-release Tablets should be equivalent to the daily dose of metformin tablets (prolonged or immediate release), up to a maximum dose of 1500mg or 2000mg respectively, given with the evening meal. After 10 to 15 days, it is recommended to check that the dose of Metformin hydrochloride 750mg or 1000mg Prolonged-release Tablets is adequate on the basis of blood glucose measurements.

In the event of transfer from another oral anti-diabetic agent: The other agent should be discontinued and titration should begin with Metformin hydrochloride 500mg Prolonged-release Tablets as indicated above, before switching to Metformin hydrochloride 750mg or Metformin hydrochloride 1000mg Prolonged –release Tablets.

Combination with insulin
Metformin and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of metformin is one 500mg prolonged-release tablet once daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

For patients already treated with metformin and insulin in combination therapy, the dose of Metformin hydrochloride 750mg or 1000mg Prolonged-release Tablets should be equivalent to the daily dose of metformin tablets up to a maximum of 1500mg or 2000mg respectively, given with the evening meal, 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	The total maximum daily dose for patients with GFR 60-89 mL/min should be the same as the currently approved dose in adults with normal renal function.	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.
30-44	1000 mg	The starting dose is at most half of the

		maximum dose.
<30	-	Metformin is contraindicated.

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).

Paediatric population
In the absence of available data, Metformin hydrochloride Prolonged-release Tablets should not be used in children.

<u>Method of administration</u>
Metformin hydrochloride Prolonged –release Tablets should be administered with food and swallowed whole with a glass of water. Metformin hydrochloride Prolonged –release Tablets should be given with the evening meal when administered once daily. The tablets should not be chewed, split or crushed.

4.3   Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
Severe renal failure (GFR <30 ml/min)
- Acute conditions with the potential to alter renal function such as:
    - dehydration,
    - severe infection,
    - shock,
- Acute or chronic disease which may cause tissue hypoxia such as:
    - cardiac or respiratory failure,
    - recent myocardial infarction,
    - shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism

4.4   Special warnings and precautions for use

<u>Lactic acidosis</u>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).

.

Diagnosis

Lactic acidosis is characterised by acidotic dysponea, , muscle cramps, asthenia abdominal pain 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 above (> 5 mmol/), and an increased anion gap and lactate/pyruvate ratio.

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.

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).

Administration of iodinated contrast agentsIntravascular administration of iodinated contrast agens may lead to contrast induced nephropathy, resulting in. T metformin accumulation an increased the riskof 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, and 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 anesthesia. 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.

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 does not cause hypoglycaemia, but 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. It is recommended that patients be advised that this is normal.

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.

Avoid consumption of alcohol or alcohol-containing medicinal products.

Iodinated contrast agent

Metformin must be discontinued prior to or at the time of the imaging procedure and restarteduntil 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.4).

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 respective medicinal product.

Diuretics, especially loop diuretics, 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 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 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 effects on the child.

Fertility

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600mg/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 meglitinides).

4.8 Undesirable effects

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

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 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.

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

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. Consideration of such 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.

<u>Reporting of suspected adverse reactions</u>
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

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: Drugs used in diabetes; blood glucose lowering drugs, excl. insulins, ATC code: A10BA02.

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.

<u>Mechanism of action</u>
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 (GLUT).

<u>Pharmacodynamic effects</u>
In clinical studies, the major non-glycaemic 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 and safety
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
After an oral dose of the prolonged-release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max} for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, C_{max} 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 C_{max} and AUC of metformin prolonged-release 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 C_{max} and T_{max} are unaffected).

Mean metformin absorption from the prolonged-release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000mg of metformin as prolonged-release tablets.

Following a single oral administration in the fed state of one tablet of Metformin 1000mg prolonged-release tablets, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours).

Metformin 1000mg prolonged-release tablets were shown to be bioequivalent to Metformin 500mg prolonged-release tablets at a 1000mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.

When the 1000mg prolonged-release tablet is administered in fed conditions the AUC is increased by 77% (C_{max} is increased by 26% and T_{max} is slightly prolonged by about 1 hour).

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 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.

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

Magnesium stearate
Silica, colloidal anhydrous
Povidone K30
Hypromellose

6.2   Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

14, 20, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 180, 600 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd.

Unit 4 The Metro Centre, Dwight Road, Watford, WD18 9SS

8 MARKETING AUTHORISATION NUMBER(S)

PL12606/0247

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12 June 2014

10 DATE OF REVISION OF THE TEXT

08/03/2019