SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bolamyn SR 500 mg Prolonged Release Tablets
(metformin hydrochloride)

Almus Bolamyn SR 500 mg Prolonged Release Tablets
(metformin hydrochloride)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 500 mg metformin hydrochloride equivalent to 390 mg metformin.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet
White to off white, oval shaped tablet, debossed with "93" on one side and "7267" on the 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. Bolamyn SR may be used as monotherapy or in combination with other oral antidiabetic agents, or 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 one 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 daily.
- Dosage increases should be made in increments of 500 mg every 10-15 days, up to a maximum of 2000 mg once daily with the evening meal. If glycaemic control is not

achieved on 2000 mg of Bolamyn SR once daily, 1000 mg of Bolamyn SR twice daily should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

- In patients already treated with metformin tablets, the starting dose of Bolamyn SR should be equivalent to the daily dose of metformin immediate-release tablets. In patients treated with metformin at a dose above 2000 mg daily, switching to Bolamyn SR is not recommended.
- If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate Bolamyn SR at the dose indicated above.

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

Elderly

Due to the potential for decreased renal function in elderly patients, 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	Additional considerations
60-89	2000 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

In the absence of available data, Bolamyn SR should not be used in children.

Method of administration

Oral use.

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.
- 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, 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.

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. The intravascular administration of iodinated contrast agents in radiologic studies can lead to renal failure. This may induce metformin accumulation which may expose to increase the risk for lactic acidosis.Metformin must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 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.

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 do not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetes (e.g. sulfonylureas 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
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 by local route) 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 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, embryonal or foetal development, parturition or post-natal 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 should 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 breast-fed 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 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.

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 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

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 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 the Yellow Card Scheme at: 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 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: Oral Blood glucose lowering drugs, excl. insulins, biguanides
ATC code: A10BA02

Mechanism of action
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.

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 (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, 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 study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes 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 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.

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 2000 mg of metformin prolonged release tablets is similar to that observed after administration of 1000 mg of metformin immediate-release tablets twice daily.

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).

Metformin absorption from the prolonged-release formulation is not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000 mg of metformin as 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.

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).

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

Hypromellose (E454)
Ethylcellulose
Cellulose, microcrystalline
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium–aluminium blisters or Aclar blisters.
Blister packs of 1, 20, 28, 30, 56, 60, 90 & 120 prolonged-release tablets.
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

TEVA UK Limited,
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex,
BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1013

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/03/2008 / 25/03/2013

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23/09/2021