Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bellformin 850 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains: Metformin hydrochloride 850 mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets
White coloured, round, biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Non-insulin-dependent diabetes (NIDDM, type II), when adequate dietary treatment has failed.
- Bellformin 850mg tablets can be given alone as initial therapy, or can be administered in combination with sulphonylureas after careful assessment of the contraindications.

4.2 Posology and method of administration

Dosage

Usual dosage:

The required daily dose ranges from 0.5 to 3g. Therapy should be initiated with a low dose of one or two tablets daily. Depending on the metabolic state the dose can be increased stepwise at intervals of a few days up to two weeks until the therapeutically required dose has been reached. In order to minimise the gastro-intestinal side-effects the daily dose should be divided and taken with or after meals. Generally, daily doses of 1.5g (two tablets) are sufficient. If diabetic control is incomplete a cautious increase in dosage to a maximum of 3g daily is justified.

No additional benefit can usually be achieved by use of doses exceeding 3g daily. Once control has been achieved it may be possible to reduce the daily dose.

In cases of metabolic decompensation:

In cases of metabolic decompensation - this should be stabilised before the administration of metformin is considered.

Children and juveniles:
Bellformin 850mg tablets are not recommended for use in children.
Bellformin 850mg tablets are not indicated for the treatment of insulin-dependent diabetes (IDDM, type I) in children and juveniles.

The use of Bellformin 850mg tablets is not advised for treatment of the very rarely occurring insulin-dependent diabetes in young adults (MODY) since no experience of its use is available.

Elderly Patients:

Bellformin 850mg tablets may be indicated in the elderly, but not when renal function is impaired.

Further dosage information

Combination with sulphonylureas:

Bellformin 850mg tablets may be used in combination with sulphonylureas if monotherapy with metformin does not lead to a satisfactory response. However, it should be noted that metformin and sulphonylureas have a different mode of action and therefore an additive or potentiating effect of these drugs might cause hypoglycaemia.

Substitution for sulphonylureas:

Bellformin 850mg tablets may be used instead of sulphonylureas in patients who formerly have been treated with sulphonylureas.

Method of Administration

Bellformin 850mg tablets should be taken unchewed together with a glass of water during or after meals.

Monitoring advice
See special warnings and special precautions for use.

4.3 Contraindications

- During pregnancy and lactation.
- In children and very old patients.
- In patients with insulin-dependent diabetes (IDDM, type I).
- In patients with non-insulin-dependent diabetes (NIDDM, type II), if sulphonylurea therapy has completely failed.
- Acidotic states during metabolic compensation.
- Precoma, hyperosmolaric or keto-acidotic coma diabeticum.
- Hypersensitivity to metformin.
- Impairment of liver and, in particular, renal functions.
- Respiratory insufficiency.
- Severe cardiovascular impairment.
- Cardiac failure and recent myocardial infarction.
- Acute severe disorders, for example infections with fever, pancreatitis or trauma.
- History of, or states associated with, lactic acidosis such as shock or pulmonary insufficiency, alcoholism (acute or chronic), and conditions associated with hypoxaemia.
- Catabolic states, e.g. in tumour diseases.
- Surgery with general anaesthesia. Metformin therapy should be stopped before, during and after surgery.
- Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such studies are planned, metformin should be discontinued at the time of, or prior to, the procedure and withheld for 48 hours subsequent to the procedure and re-instituted only after renal function has been re-evaluated and found to be normal.
- Reduced diet (< 1000 kcal or 4200 kJ per day).

4.4 Special warnings and precautions for use

Warnings

- In patients with impaired liver function, lactate clearance may be restricted.
- The risks of lactic acidosis and accumulation are determined by renal function. Therefore, metformin therapy

requires a normal renal function, which should be regularly reviewed.

- During concomitant therapy with sulphonylureas or insulin, blood glucose levels should be monitored because combined therapy may cause hypoglycaemia. Stabilisation of diabetic patients with metformin and insulin should be carried out in a hospital until the correct ratio of the two drugs has been obtained.
- Patients receiving continuous metformin therapy should have an annual estimation of Vitamin B_{12} levels because of reports of decreased Vitamin B_{12} absorption.

Precaution for use

- The use of metformin is not advised in conditions which may cause dehydration or in patients suffering from serious infections or trauma.
- Patients who suddenly suffer from muscle spasms, dyspepsia, abdominal pain and fatigue should consult a physician immediately, since these symptoms may indicate lactic acidosis. Lactic acidosis is accompanied by acidotic dyspnoea, abdominal pain, hyperthermia, comatose state, decrease of blood pH value and increase of lactate value.
- Serum creatinine levels should be determined before and four weeks after metformin therapy has been started. Regular measurements should take place once or twice a year unless required earlier due to intercurrent disorders. In the elderly, creatinine clearance is advised before the onset of metformin therapy.

4.5 Interaction with other medicinal products and other forms of interaction

- During treatment with Bellformin 850 mg tablets alcohol has to be strictly avoided. Acute and chronic alcohol abuse may increase the blood glucose decreasing effect and the serum lactate increasing effect of metformin to unpredictable extents.
- Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such studies are planned, metformin should be discontinued at the time of, or prior to, the procedure and withheld for 48 hours subsequent to the procedure and re-instituted only after renal function has been re-evaluated and found to be normal.
- Metformin therapy should also be stopped two days before and two days after surgery with general anaesthesia.

Precautions for Use

An increase of the antihyperglycaemic effect of metformin is possible in the event of concomitant administration with medicinal products for the same indication, for example:

- Insulin.
- Oral antidiabetic drugs, of the sulphonylurea and acarbose.

An increase of the antihyperglycaemic effect of metformin is also possible in the event of concomitant administration with medicinal products for other indications which possess blood glucose-lowering effects of their own, for example:

- Non steroidal anti-inflammatory drugs (NSAIDs), e.g. salicylates or pyrazolones.
- Monoamine oxidase (MAO) inhibitors.
- Oxytetracycline.
- Angiotensin converting enzyme (ACE) inhibitors.
- Clofibrate derivatives.
- Cyclophosphamide and its derivatives.

$\Rightarrow$ The combination of metformin and the above mentioned drugs can induce hypoglycaemia.

Moreover, during permanent therapy, beta-blockers and antisympathotonic drugs, such as clonidine, reserpine or guanethidine, may decrease blood glucose levels. However, of particular clinical relevance is their reducing action on the hormonal and neural counterregulation during hypoglycaemia, which in turn may impair the subjective perception of hypoglycaemic warning signs.

A decrease of the antihyperglycaemic effect of metformin in combination with one of the following drugs may occur:

- Glucocorticoids.
- Estrogen-Gestagen-Combinations.
- Adrenaline and other Sympathomimetics.
- Glucagon.
- Thyroid hormones.
- Thiazides and loop diuretics.
- Diazoxide.
- Phenothiazines.
- Nicotinic acid derivatives.

Guar:	A decrease of the absorption of metformin may lead to an attenuation of metformin effects.
Cimetidine:	Substances which delay the elimination of metformin, e.g. cimetidine, may increase the risk of lactic acidosis.
Anticoagulants:	Elimination of anticoagulants e.g. coumarins may be accelerated during metformin therapy. Therefore the blood coagulation inhibiting effect may be decreased and frequent controls of blood coagulation are necessary.

To be taken into account

During maintenance therapy the onset or termination of any other additional therapy can disturb the control of diabetes.

4.6 Pregnancy and lactation

During pregnancy the administration of Bellformin 850 mg tablets are contraindicated. The use of Bellformin 850 mg tablets should be avoided in women who are breast-feeding. No information is available on whether metformin or its metabolites are excreted in the breast milk.

4.7 Effects on ability to drive and use machines

When Bellformin 850 mg tablets are used as monotherapy, hypoglycaemia is not usually a problem and does not influence the ability to drive or operate machinery. In cases of combined therapy with sulphonylureas or other drugs with blood glucose lowering effects, hypoglycaemia may occur and, hence, such combinations may produce minor or moderate adverse effects. Patients undergoing such combination therapy should be advised to take precautions to avoid hypoglycaemia whilst driving or operating machinery.

4.8 Undesirable effects

Frequently arising undesirable effects are: Gastro-intestinal disturbances.

- Bellformin 850 mg tablets is normally well tolerated, but at the beginning of metformin therapy gastro-intestinal disturbances, such as nausea, vomiting, abdominal pain, diarrhoea, anorexia and metallic taste occur in 5-20% of patients. These gastro-intestinal disturbances are generally of minor importance and require no termination of metformin therapy. The frequency and severity of these gastro-intestinal disturbances can be reduced markedly by starting with low and gradually increasing metformin doses and by administration of metformin with or after meals.
- About 5% of all patients do not tolerate metformin therapy.

Very rarely arising undesirable effects are:
- Hypersensitivity and lactic acidosis.
- Hypersensitivity reactions of the skin.

- Lactic acidosis.

With metformin therapy lactic acidosis with coma and death is possible. Lactic acidosis induced by metformin is accompanied by impaired hepatic lactate clearance and increased muscular lactate release. Although metformin - induced lactic acidosis occurs very rarely (until now only 100 incidents world-wide) the mortality reaches 50%.

Causes of lactic acidosis:
The following may predispose to lactic acidosis: Renal insufficiency, impaired liver function, alcohol consumption, other diseases with effect on the oxidative metabolism, for example cardiac decompensation or severe infections and catbolic conditions as well as interactions with other drugs.

Symptoms of lactic acidosis:
At first lactic acidosis resembles the gastro-intestinal side-effects of metformin, for example nausea, vomiting, diarrhoea and abdominal pain. However, within a few hours the complete clinical picture of lactic acidosis with muscle pains, hyperventilation, clouding of consciousness and coma may develop. On suspicion of lactic acidosis metformin therapy must be immediately stopped and the patient must be treated at once as an emergency in a hospital.

Reported single cases:

- Inhibition of the absorption of Vitamin B_{12} or folic acid may cause megaloblastic anaemia. Patients receiving continuous metformin therapy should have an annual estimation of Vitamin B_{12} levels.
- Persisting gastro-intestinal disturbances require the termination of metformin therapy.

4.9 Overdose

Human experience

Intoxication with Bellformin 850 mg tablets does not lead to hypoglycaemia but lactic acidosis may develop. Usually, the cause is not overdosage, but accumulation as a result of impaired renal function and, at the same time, inadequate dose adjustment.
Hypoglycaemia can occur when Bellformin 850 mg tablets are given concomitantly with sulphonylureas, alcohol or insulin.

Management of overdosage in man

If signs of lactic acidosis or of metformin overdosage, for example in suicidal intention, are shown, patients must be admitted to a hospital as an emergency. The diagnosis of lactic acidosis should be confirmed by determination of lactate and if possible metformin concentrations. Haemodialysis is the most effective measure to eliminate lactate and metformin. Symptomatic treatment includes circulatory stabilisation, compensation of acidosis and elimination of hypoxia. The metformin concentration in erythrocytes is a good indicator for accumulation and can be used to decide whether repeated haemodialysis is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Metformin is a biguanide oral antihyperglycaemic agent (ATC Code A10B A02) and reduces elevated blood glucose levels only in patients with non-insulin-dependent diabetes (NIDDM) (type II diabetes mellitus), but does not increase insulin secretion and does not cause hypoglycaemia or increased weight gain. Its mode of action is multifactorial and not yet completely understood. However, the augmentation of glucose uptake into peripheral tissues may influence glucose utilisation. Furthermore, the effects of metformin include reduced hepatic gluconeogenesis and delayed intestinal glucose absorption which may explain the blood glucose-lowering effect. The efficacy of metformin is dependent on a minimum concentration of insulin.

Metformin seems to potentiate insulin action by enhancing insulin binding to its receptors and by facilitating steps in

the post-receptor pathways of insulin-action. Apart from the glucose-lowering effect, metformin reduces the serum triglyceride level and possesses antithrombotic properties.

5.2 Pharmacokinetic properties

After oral administration metformin is incompletely absorbed from the gastro-intestinal tract. The oral bioavailability of usual doses is 50-60%. The maximum plasma concentration is achieved after about 2 hours. Gastrointestinal absorption is complete within 6 hours of ingestion. The volume of distribution lies between 63 and 276 litres. Metformin is rapidly distributed but a slow transfer to a deep compartment seems to occur. Metformin does not bind to plasma proteins but accumulates in the salivary glands, duodenum, kidneys and liver. No metabolites or conjugates of metformin have been identified. Metformin is completely eliminated by renal excretion and the mean plasma elimination half-life ranges between 1.5 and 4.5 hours.

A quantitatively minor terminal elimination phase, probably out of the deep compartment, with a longer mean half-life, ranging from 8.9 to 19 hours, has been observed. The renal clearance of metformin ranges between 350 and 550 ml/min and correlates with the creatinine clearance, indicating that metformin is excreted by active tubular secretion. In patients with impaired renal function accumulation of metformin is probable.

5.3 Preclinical safety data

Acute toxicity:

Acute toxicity after different routes of administration and in different animals was investigated. The data indicate the highest toxicity of metformin hydrochloride after subcutaneous administration to guinea pigs and rabbits (LD_{50} = 150 mg/kg) and intravenous administration to mice (LD_{50} = 180 mg/kg).

The toxicity after oral ingestion of metformin hydrochloride seems to be several times lower, rabbits and guinea pigs (LD_{50} 350 and 500 mg/kg, respectively) being more sensitive than mice or rats (LD_{50} 1450 mg/kg and 1000 mg, respectively). Hence, in various animal species studied, after different routes of administration the LD_{50} values are considerably above the therapeutic dose range in humans (maximum approximately 40 mg/kg/day).

Chronic toxicity:

Studies with repeated administration of metformin to rats (up to 18 months), dogs (up to 18 months) and monkeys (up to 2 years) revealed no specific toxic effects.

Mutagenic and carcinogenic effects:

Bacterial tests for mutagenicity of metformin were negative but chromosomal alterations were observed *in vitro* in mammalian cells. The relevance of these effects remains obscure. Long-term animal studies failed to detect any oncogenic properties of metformin.

Reproductive toxicity:

No teratogenic properties of metformin have been found in rats. The no adverse-effect level (NOAEL) of metformin in rats was estimated to be 300 mg/kg/day for embryotoxicity and female reproduction and up to 600 mg/kg/day for male fertility. No teratogenic effects were observed in rabbits with doses up to 140 mg/kg/day (p.o.). In rats doses up to 600 mg/kg/day administered p.o. pre- and postnatally showed no effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Sodium starch glycolate (Type A)
Maize starch
Povidone
Colloidal anhydrous silica
Magnesium stearate

Film-coating:
Hypromellose
Titanium dioxide (E171)
Propylene glycol (E1520)
Macrogol 6000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25˚C. Store in the original package.

6.5 Nature and contents of container

Blister strips consisting of PVC/PE/PVDC – Aluminium foil containing 56 film – coated tablets in an outer carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

BellPharma Limited
First Floor
69 St. Patrick’s Road
Dalkey
County Dublin

8 MARKETING AUTHORISATION NUMBER

PA 1185/1/2

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