For the use only of Registered Medical Practitioner or a Hospital or a Laboratory.

SPANBEC–M | SPANBEC – M FORTE®

(Glimepiride + Metformin)

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DESCRIPTION:

SPANBEC-M/ SPANBEC-M Forte (Glimepiride+Metformin HCl) contains two oral antihyperglycemic agents withcomplementarymechanism of action to improve glycemic control with type 2 diabetes.

QUALITATIVE & QUANTITATIVE COMPOSITION:

SPANBEC-M (Glimepiride + Metformin HCl) is available for oral administration as:

SPANBEC-M1: Each bilayeredun coated tablet contains: Metformin HCl 500mg (in extended release form) & Glimepiride 1 mg.

SPANBEC-M2: Each bilayeredun coated tablet contains: Metformin HCl 500 mg (in extended release form) & Glimepiride 2 mg.

SPANBEC-M1 FORTE: Each bilayered uncoated tablet contains: Metformin Hydrochloride 1000 mg (in extended release form) & Glimepiride 1 mg.

SPANBEC-M2 FORTE: Each bilayered uncoated tablet contains: Metformin Hydrochloride 1000 mg (in extended release form) & Glimepiride 2 mg.

CLINICAL PHARMACOLOGY:

Mechanism of Action

Glimepiride:

Glimepiride primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Sulfonylureas bind to the sulfonylurea receptor in the pancreatic beta-cell plasma membrane, leading to closure of the ATP-sensitive potassium channel, thereby stimulating the release of insulin.

Metformin HCl:

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

Metformin HCl may act via three mechanisms;

- By reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- In muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilization
- By delaying intestinal glucose absorption.

Pharmacokinetics:

Absorption:

Glimepiride: Following oral administration of a 100mg dose, Sitagliptin absorbs rapidly withPeak plasma concentration (median Tmax) occurring 1 to 4 hours post-dose, mean plasma AUC of Sitagliptin is 8.52 µMhr, with Cmax 950nM. The absolute bioavailability of Sitagliptinis approximately 87%. Plasma AUC of Sitagliptin increased in a dose-proportional manner.

Metformin HCl: After an oral dose of Metformin HCl, Tmax is reached in 2.5 hrs. The absolute bioavailability of a single dose 500mg dose is reported to be about 50% to60% given under fasting condition. Single oral doses of Metformin HCl tablets500mg to 1500mg, that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent and slightly delays the absorption of Metformin, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC). The pharmacokinetics of Metformin HCl absorption is non-linear.

Distribution:

Glimepiride: After intravenous dosing in healthy subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metformin HCl: Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Metformin HCl tablets, steady-state plasma concentrations of Metformin are reached within 24-48 hours and are generally <1 mcg/mL. Maximum Metformin HCl plasma levels do not exceed 5mcg/mL, even at maximum doses.

Metabolism:

Glimepiride: Glimepiride is completely metabolized by oxidative biotransformation after either an intravenous or oral dose. The major metabolites are the cyclohexylhydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 is involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M2 is inactive. In animals, M1 possesses about one-third of the pharmacological activity of glimepiride, but it is unclear whether M1 results in clinically meaningful effects on blood glucose in humans.

Metformin: Metformin is not metabolized.

Mechanism of Excretion:

Glimepiride: Approximately 60% of the total radioactivity was recovered in the urine in 7 days. M1 and M2 accounted for 80-90% of the radioactivity recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces. M1 and M2 accounted for about 70% (ratio of M1 to M2 was 1:3) of the radioactivity recovered in feces. No parent drug was recovered from urine or feces.

Metformin HCl: It is cleared from the body by tubular secretion and excreted unchanged in the urine; metformin is undetectable in blood plasma within 24 hours of a single oral dose. The average elimination half-life in plasma is 6.2 hours.

Pharmacokinetics of SPANBEC - M with the fixed dose of glimepiride and metformin: In case of administration of fixed dose of the combined drug SPANBEC - M (tablet containing glimepiride 2 mg + metformin 500 mg), Cmaxand AUC values correspond to bioequivalence criteria when compared to the same parameters in case of administration of the samecombination as separate preparations (tablet of glimepiride 2 mg and metformin 500 mg).In addition, dose-proportional increase of Cmaxand AUC of glimepiride was shown by increasingthe dose from 1 mg to 2 mg in the combined fixed-dose preparations with a constant dose ofmetformin (500 mg) in the composition of these preparations.No other significant differences are observed in safety, including profile of adverse effects inpatients taking the drug 1 mg +500 mg, and the patients taking the drug 2 mg +500 mg.

THERAPEUTIC INDICATIONS:

Treatment of diabetes mellitus type 2 (in addition to diet, physical exercise and weight loss):When glycemic control cannot be achieved with metformin or glimepiridemonotherapy.

DOSAGE AND ADMINISTRATION:

Typically the dose of medicine SPANBEC – M should be determined by the target glucose concentration in blood. It is necessary to take the lowest dose that would be sufficient to achieve the desired metabolic control. During treatment with medicine SPANBEC – M, concentration of glucose in blood should be regularly determined. In addition, regular control of percentage of glycated hemoglobin is also recommended. Incorrect administration of the medicine, such as skipping of the next dose, should never be replenished by subsequent administration of higher doses. Actions of the patient in case of mistakes while taking the medicine (in particular in case of skipping of the next dose of SPANBEC – M or skipping of a meal), or in the situations where there is no possibility to take the medicine, should be consulted in advance between the patient and the physician. Since improvement in metabolic control is associated with increased sensitivity of tissues to insulin, the need for glimepiride may decrease in the course of treatment with SPANBEC – M. In order to avoid development of hypoglycemia, the dose should be promptly reduced or administration of SPANBEC – M should be stopped. SPANBEC – M should be taken once or twice a day during a meal. Maximum single dose of metformin is 1000 mg. Maximum daily dose: 8 mg - for glimepiride and 2 000 mg – for metformin. Only for a small number of patients more effective daily dose is more than 6 mg of glimepiride. Initial dose of SPANBEC – M should not exceed daily dose of glimepiride and metformin already being taken by a patient in order to avoid hypoglycemia. When transferring patients taking the combination of glimepiride and metformin monotherapies to SPANBEC – M, dose of SPANBEC – M will be determined on the basis of doses of glimepiride and metformin taken already, as separate preparations. If increase of the dose is necessary, daily dose of SPANBEC – M should be titrated in increments of only 1 tablet of SPANBEC – M 1 mg + 250 mg or ½ tablet of SPANBEC – M 2 mg + 500 mg.

Duration of treatment: Typically, treatment with SPANBEC – M is carried out for a long time. Use in pediatric patients: Safety and efficacy of the medicine was not studied in children with diabetes mellitus type 2.

Use in elderly patients: Metformin is excreted mainly by the kidneys. Since there is the risk of development of severe adverse reactions to metformin in patients with impaired renal function, the medicine can only be used in patients with normal renal function. Due to the fact that renal function is reduced with age, metformin

should be used with caution. You should carefully select the dose and ensure thorough and regular monitoring of renal function.

ADVERSE REACTIONS:

Glimepiride: Metabolism and nutrition disorders: Hypoglycemia: As a result of the blood-glucose-lowering action of this drug, hypoglycemia may occur, which-based on what is known of other sulfonylureas- may also be prolonged. In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris, and cardiac arrhythmias. The clinical picture of a severe hypoglycemic attack may resemble that of a stroke. The symptoms nearly always subside when hypoglycemia is corrected.

Eye disorders: Especially at the start of treatment, there may be temporary visual impairment due to the change in blood glucose levels. The cause is a temporary alteration in the turgidity and hence the refractive index of the lens, this being dependent on blood glucose level.

Gastrointestinal disorders: Occasionally, gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhoea may occur.

Hepatobiliary: In cases, elevation of liver enzymes levels and impairment of liver function (e.g., cholestasis and jaundice) may occur, as well as hepatitis which may progress to liver failure.

Blood and lymphatic system disorders: Changes in the blood picture may occur: Rarely, thrombocytopenia and, in isolated cases, leucopenia, haemolyticanaemia, erythrocytopenia, granulocytopenia, agranulocytosis or pancytopenia may develop. Because it is reported that aplastic anemia and pancytopenia may occur in sulfonylureas, careful monitoring should be performed. If these occur, the medication should be discontinued and adequate treatment taken. Cases of severe thrombocytopenia with platelet count less than 10,000/µl and thrombocytopenic purpura have been reported in post-marketing experience.

Skin and subcutaneous tissue disorders: Alopecia.

General disorders: Occasionally, allergic or pseudo-allergic reactions (e.g., itching, urticaria, or rashes) may occur. These reactions are almost mild but may develop into serious reactions with dyspnoea and a fall in blood pressure, sometimes progressing to shock. In the event of urticaria a physician must therefore be notified immediately.

Investigations: Glimepiride, like all sulfonylureas, can cause weight gain.

Metformin: Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to this drug and are approximately 30% more frequent in patients on monotherapy than in placebo-treated patients, particularly during initiation of this drug therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful. In clinical trials, this drug was discontinued due to GI reactions in approximately 4% of patients. Because GI symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take this drug with meals. Because significant diarrhea and/or vomiting may cause dehydration and prerenal azotemia, under such circumstances, this drug should be temporarily discontinued. For patients who have been stabilized on this drug, nonspecific GI symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis has been excluded.

Special senses: During initiation of this drug therapy, approximately 3% of patients may complain of an unpleasant or metallic taste, which usually resolve spontaneously. Skin reactions such as erythema, pruritus, urticarial are very rare.Lactic acidosis is very rare.

CONTRAINDICATIONS:

- Insulin-dependent (type I) diabetes (e.g., diabetics with a history of ketonemia), diabetic ketonemia, diabetic coma or precoma, acute or chronic metabolic acidosis.
- Known hypersensitivity to any of the excipients of this drug, sulfonylureas, sulfonamides, or biguanide.
- There is no experience in patients with severe hepatic dysfunction or hemodialysis. In case of severe hepatic or renal function disorders, a change-over to insulin is required to achieve adequate control of blood glucose.
- Pregnant women, women of child-bearing potential, nursing mother.
- Patients susceptible to lactic acidosis, patients with a history of lactic acidosis, renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females], or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
- This drug should be temporarily discontinued in patients being administered iodinated contrast materials intravenously, because use of such products may result in acute alteration of renal function.
- Severe infections, before and after surgery, serious trauma.
- Malnourished, starving, or debilitated patients, or patients with pituitary or adrenal insufficiency.
- Hepatic dysfunction, severe lung dysfunction, other condition likely to be with hypoxemia, excessive alcohol intake, dehydration, gastrointestinal disturbance including diarrhea and vomiting.
- Congestive heart failure requiring pharmacologic treatment.

Use in Pregnancy & Lactation:

Pregnancy: For Glimepiride: This drug must not be taken during pregnancy. Otherwise there is risk of harm to the child. Pregnant patient or the patient planning a pregnancy must inform their physician. It is recommended that such patients change over to insulin.

For Metformin: 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 fetal development, parturition or postnatal development.

However, 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.

Lactation: For Glimepiride: To prevent possible ingestion with the breast milk and possible harm to the child, glimepiride must not be taken by breast-feeding women. If necessary the patient must change over to insulin, or must stop breast-feeding.

For Metformin: Metformin is excreted into milk in lactating rats. 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 should be made on whether to discontinue nursing or to discontinue metformin, taking into account the benefit and potential risk of adverse effect on the child and importance of the compound to the mother.

PRECAUTIONS:

Monitoring of renal function: Metformin HCl-related lactic acidosis increases with the degree of insufficiency of renal function, therefore, serum creatinine concentrations should be determined regularly.

Impaired hepatic function: Since impaired hepatic function has been associated with some cases of lactic acidosis, Glimepiride+Metformin HCl should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Hypoglycemia: Patient receiving Glimepiride+Metformin HCl in combination withinsulin may be at risk for hypoglycemia. Therefore, a reduction in the dose of the sulphonylurea or insulin may be necessary.

Metformin HCl: Lactic acidosis It is a very rare, but serious, metabolic complication can occur due to MetforminHCl accumulation. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalized immediately.

Administration of iodinated contrast agent: The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure which has been associated with lactic acidosis in patients receiving Metformin HCl. Therefore, Glimepiride + Metformin HCl should 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.

DRUG INTERACTIONS:

Glimepiride: Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9).). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g., rifampicin) or inhibitors (e.g., fluconazole).

Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example: insulin and other oral antidiabetics; ACE inhibitors; allopurinol; anabolic steroids and male sex hormones; chloramphenicol; coumarin derivatives; cyclophosphamide; disopyramide; fenfluramine; fenyramidol; fibrates; fluoxetine;

guanethidine; ifosfamide; MAO inhibitors; miconazole; fluconazole; para-aminosalicylic acid; pentoxifylline (high dose parenteral); phenylbutazone; azapropazone; oxyphenbutazone; probenecid; quinolones; salicylates; sulfinpyrazone; clarithromycin; sulfonamide antibiotics; tetracyclines; tritoqualine; trofosfamide.

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following drugs is taken, for example: acetazolamide; barbiturates; corticosteroids; diazoxide; diuretics; epinephrine (adrenaline) and other sympathomimetic agents; glucagon; laxatives (long term use); nicotinic acid (in high doses); oestrogens and progestogens; phenothiazines; phenytoin; rifampicin; thyroid hormones. H2 receptor antagonists, clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect. Beta-blockers reduce glucose tolerance. Reduction of glucose tolerance may change metabolic control. Beta-blockers may increase the risk of hypoglycemia (due to failure of counter-regulation). Under the influence of sympatholytic drugs such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent. Both acute and chronic alcohol intake may potentiate or weaken the blood-glucose-lowering action of glimepiride in an unpredictable fashion. The effect of coumarin derivatives may be potentiated or weakened.

Bile acid sequestrant: Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction was observed when glimepiride was taken at least 4 hours before colesevelam. Therefore glimepiride should be administered at least 4 hours prior to colesevelam.

Metformin: Concomitant use not recommended: Alcohol: Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic insufficiency. Avoid consumption of alcohol and alcohol-containing medications. Iodinated contrast agents: Metformin should be discontinued at the time of or prior to the procedure, and withheld for 48hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Combinations requiring precautions for use: Medicinal products with intrinsic hyperglicaemic activity (e.g. glucocorticoids and tetracosactides (systemic and local routes), beta-2-agonists, danazol, and chlorpromazine at high dosages of 100 mg per day, diuretics): 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. Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function.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.

Others: Lactic acidosis may occur by concomitant administration with antibiotics having strong nephrotoxicity (gentamicin, etc).

The hypoglycemic action of co-administration with the following drugs may be potentiated or weakened. When these drugs are administered, the blood glucose level and patient should be observed closely. Drugs potentiating the effect Insulin, sulfonamides, and sulfonylureas products, Anabolic steroids, guanethidine, salicylates (aspirin, etc), beta-blockers(propranolol, etc), MAO inhibitors. Drugs weakening the effect. Epinephrine, corticosteroids, thyroid hormones, estrogens, diuretics, pyrazinamide, isoniazid, nicotinic acid, phenothiazines.

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the Cmax and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin Cmax and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. Metformin had minimal effects on nifedipine.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving metformin, the patient should be closely observed to maintain adequate glycemic control.

OVERDOSAGE:

For Glimepiride: Acute overdosage as well as long-term treatment with too high a dose of glimepiride may lead to severe life-threatening hypoglycaemia.In case of overdosage with glimepiride, a doctor must be notified immediately. At the first signs of hypoglycaemia, the patient must immediately take sugar, preferably glucose, unless a doctor has already started care. Since hypoglycaemia and its clinical symptoms may recur after apparent clinical recovery (even after several days), close and continued medical supervision and possibly referral to a hospital are indicated. In particular, significant overdosage and severe reactions, e.g. with unconsciousness or other neurological dysfunctions, are emergency cases and require immediate care and hospitalization. If hypoglycaemic coma is diagnosed or suspected, intravenous infusion of a 20 % glucose solution (adults: 40 to 100 ml) is indicated. Alternatively IV, SC, or IM administration of glucagons (adults: 0.5 to 1 mg) may be considered. In infants, glucose must be dosed very carefully and close monitoring of blood glucose is required to minimize the risk of potentially severe hyperglycaemia. Patients who have ingested life-threatening amounts of glimepiride require detoxification (e.g. by gastric lavage and medicinal charcoal). After acute glucose replacement has been completed it is usually necessary to give an intravenous glucose infusion in lower concentration so as to ensure that the hypoglycaemia does not recur. The patient's blood glucose level should be carefully monitored for at least 24 hours. In severe cases with a protracted course, hypoglycaemia, or the danger of slipping back into hypoglycaemia, may persist for several days.

For Metformin: 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. Metformin is dialyzable with a clearance of up to 170mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.Pancreatitis may occur in the context of a metformin overdose.

PRODUCT PRESENTATION:

SPANBEC-M & SPANBEC-M FORTE tablets are available as:

- Glimepride 1mg + Metformin 500mg (bilayered uncoated tablets)
  Packaging: 10 Tablets X 10 Blisters
- Glimepride 2mg + Metformin 500mg (bilayered uncoated tablets)
  Packaging: 10 Tablets X 10 Blisters
- Glimepride 1mg + Metformin 1000mg (bilayered uncoated tablets)
  Packaging: 10 Tablets X 10 Blisters
- Glimepride 2mg + Metformin 1000mg (bilayered uncoated tablets)
  Packaging: 10 Tablets X 10 Blisters

ID: 01 pi MEG 20

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