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INSTRUCTION
for medical use

DUGLIMAX®

Composition:
active substances: metformin hydrochloride, glimepiride;
1 tablet contains metformin hydrochloride (long-acting) 500 mg and glimepiride 1 mg or metformin hydrochloride (long-acting) 500 mg and glimepiride 2 mg;
excipients (tablets 500 mg/1 mg): sodium carboxy methyl cellulose, hypromellose, microcrystalline cellulose, magnesium stearate, lactose monohydrate, croscarmellose sodium, hydroxy propyl cellulose, iron oxide red (E 172);
excipients (tablets 500 mg/2 mg): sodium carboxy methyl cellulose, hypromellose, microcrystalline cellulose, magnesium stearate, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, Pigment Blend PB-51323 green.

Pharmaceutical form. Tablets.
Basic physical and chemical properties:
Duglimax® (500 mg/1 mg): a two-layer capsule-shaped, biconvex tablet pink on one side, white on the other side, smooth on both sides; mottling is allowed;
Duglimax® (500 mg/2 mg): a two-layer, capsular-shaped, biconvex tablet green on one side, white on the other side, smooth on both sides; mottling is allowed.

Pharmacotherapeutic group.
Antidiabetic drugs. Combination of oral hypoglycemic drugs.
ATC code A10B D02.

Pharmacological properties.
Pharmacodynamics.
Glimepiride is a substance that has hypoglycemic activity upon oral administration and belongs to the group of sulfonylurea derivatives. It may be used in non-insulin-dependent diabetes mellitus.
Glimepiride acts mainly by stimulating insulin release from pancreatic β-cells. Like other sulphonylureas, it increases the responsiveness of the pancreatic β-cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects similarly to other sulphonylureas.

Insulin release.
Sulphonylurea regulates insulin secretion by closing the ATP-sensitive potassium channels in the β-cell membrane. Such closure induces depolarization of the cell membrane, resulting in the opening of calcium channels and in an increased influx of calcium into the cell.
This stimulates insulin release through exocytosis.
Glimepiride binds with high affinity to a β-cell membrane protein associated with the ATP-sensitive potassium channel, but in a site different from the usual sulphonylurea binding site.
Extrapancreatic activity.
Extrapancreatic effect lies in particular in increasing the sensitivity of peripheral tissue to insulin and decreasing insulin uptake by the liver.
Glucose is transported from blood to peripheral muscle and fat tissues through special transport proteins, localized on the cellular membrane. The transportation of glucose to these tissues is the stage that limits the glucose uptake rate. Glimepiride increases very rapidly the number of active glucose transporters on the plasma membranes of muscle and fat cells, as a result stimulating glucose uptake.
Glimepiride increases the activity of the glycosyl-phosphatidylinositol-specific phospholipase C which may be correlated with the drug-induced lipogenesis and glycogenesis in isolated fat and muscle cells.
Glimepiride inhibits glucose production in the liver by increasing the intracellular concentration of fructose-2,6-bisphosphate, which in its turn inhibits gluconeogenesis.
Metformin.
Metformin is a biguanide with hypoglycemic effects, lowering both the basal and postprandial plasma glucose levels. It does not stimulate insulin secretion and therefore does not lead to hypoglycemia.
The action of metformin lies in:
- reducing hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis;
- in muscles – increasing insulin sensitivity, improving peripheral glucose uptake and utilization;
- delaying intestinal absorption of glucose.
Metformin stimulates intracellular glycogen synthesis by affecting glycogen synthase.
Metformin increases the transport capacity of specific membrane glucose transporters (GLUT-1 and GLUT-4).
Metformin affects lipid metabolism in patients irrespective of blood glucose levels. This has been demonstrated when using the product in therapeutic doses during controlled medium-term and long-term clinical studies: metformin reduces the total cholesterol, LDL (low-density lipoproteins) and triglyceride levels.
Pharmacokinetics.
Glimepiride.
Absorption.
The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant effect on absorption, only the absorption rate is slightly diminished. C_{max} is reached approximately 2.5 hours following oral intake (mean 0.3 µg/ml following multiple dosing of 4 mg daily). There is a linear relationship between the dose and both C_{max} and AUC.
Distribution.
Glimepiride has a very low distribution volume (approximately 8.8 litres) which is roughly equal to the distribution volume of albumin, has a high degree of blood protein binding (> 99 %), and a low clearance (approx. 48 ml/min).
In animals, glimepiride is excreted in milk. Glimepiride crosses the placenta. Penetration of the blood-brain barrier is low.
Biotransformation and elimination.
The mean half-life which depends on serum concentrations under multiple-dose conditions, is about 5-8 hours. After high doses, slightly longer half-lives were observed.
After a single dose of radiolabeled glimepiride, 58 % was recovered in the urine, and 35 % in the feces. No unchanged substance was detected in the urine. Two metabolites, most likely resulting from hepatic metabolism (the major enzyme responsible for biotransformation is the CYP2C9 cytochrome),

were excreted both in the urine and feces: the hydroxy derivative and the carboxy derivative. Following oral administration of glimepiride, the terminal half-lives of these metabolites were 3-6 and 5-6 hours respectively.
Comparison of single and multiple dosing revealed no significant differences in pharmacokinetics, and the intraindividual variability was very low. No relevant accumulation was observed.
The pharmacokinetics were similar in males and females, as well as in young and elderly (over 65 years of age) patients. In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for mean serum concentrations to decrease, most likely resulting from a more rapid elimination due to lower protein binding. Renal elimination of the two metabolites was impaired. Overall no additional risk of accumulation was observed in such patients.
The pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy volunteers.
Metformin.
Absorption.
After an oral dose of metformin, the time to maximum plasma concentrations (t_{max}) is 2.5 h. Absolute bioavailability of a 500 mg metformin dose is approximately 50-60 % in healthy volunteers. After an oral dose, the non-absorbed fraction recovered in the feces was 20-30 %.
Following oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 hours and are generally less than 1 μg/mL. In controlled clinical trials, the C_{max} of metformin in blood plasma did not exceed 4 μg/mL, even at maximum doses.
Food intake decreases the extent and slightly prolongs the absorption time of metformin. Following administration of a 850 mg dose with food, a 40 % decrease of plasma C_{max}, a 25 % decrease in AUC and a 35 min prolongation of t_{max} was observed. The clinical relevance of such changes is unknown.
Distribution.
Plasma protein binding is negligible. Metformin is distributed in erythrocytes. The blood C_{max} is lower than the plasma C_{max} and is reached in approximately the same time. Erythrocytes most likely represent a secondary compartment of distribution. The mean Vd ranges between 63-276 L.
Biotransformation and elimination.
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.
Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the terminal elimination half-life is approximately 6.5 hours. If 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 plasma levels of metformin.

Clinical characteristics.
Indications.
As an addition to diet and physical exercise in patients with non-insulin-dependent diabetes mellitus (type II):
- if monotherapy with glimepiride or metformin does not provide appropriate glycemic control;
- when replacing combination therapy with glimepiride and metformin.

Contraindications.
- Insulin-dependent type I diabetes mellitus (for example, diabetes mellitus with a history of ketonemia), diabetic ketonemia, diabetic coma and pre-coma, acute or chronic metabolic acidosis.
- Hypersensitivity to any of the excipients of this medicinal product, or to sulfonylureas, sulfanilamides or biguanides.
- Hepatic insufficiency, severe hepatic function disorders, undergoing hemodialysis (no experience has so far been gained concerning the use of the drug in such cases). In case of severe liver and kidney

function disorders, in order to achieve proper glycemic control, the patient should be changed over to insulin.
- Pregnancy; possible pregnancy; breastfeeding.
- Predisposition to lactic acidosis, history of lactic acidosis, renal failure or renal dysfunction (as evidenced, for example, by decrease of plasma creatinine levels ≥ 1.5 mg/dl for men and ≥ 1.4 mg/dl for women or abnormal creatinine clearance), which can also be caused by such conditions as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
- Radiologic tests involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT)): intravascular iodinated contrast materials can lead to acute renal dysfunction and lactic acidosis in patients receiving metformin. Therefore, in patients for whom any such test is planned, the drug Duglimax® should be temporarily discontinued 48 hours prior to the procedure. Treatment should be reinstituted only after renal function has been reevaluated and found to be normal. Besides, the drug is contraindicated in patients with acute symptoms with the potential to alter renal function (dehydration, severe infection, shock).
- Severe infections, conditions before and after surgical interventions, serious injury. The use of the drug should be temporarily postponed at the time of any surgical procedure (except for minor procedures that do not require restrictions of food and water intake). The medicinal product should not be resumed until the patient resumes oral nutrition and the renal function returns to normal.
- Malnutrition, fasting or exhaustion of the patient.
- Pituitary or adrenal insufficiency.
- Hepatic dysfunction (since lactic acidosis has been reported with hepatic dysfunction, the use of this medicinal product should generally be avoided in patients with clinical or laboratory signs of liver disease), pulmonary infarction, severe pulmonary dysfunction and other conditions that may be associated with hypoxemia (such as cardiac or respiratory failure, recent myocardial infarction, shock), excessive alcohol consumption, dehydration, gastrointestinal disorders, including diarrhea and vomiting.
- Severe renal impairment (glomerular filtration rate (GFR) < 30 mL/min).
- Congestive heart failure requiring medication; recent myocardial infarction; severe cardiovascular collapse or respiratory failure.

Interaction with other medicinal products and other forms of interaction.
Glimepiride.
When other drugs are concomitantly administered to or withdrawn from a patient receiving the drug Duglimax®, both undesired increases and decreases in the hypoglycemic action of glimepiride can occur. Based on experience with the drug Duglimax® and with other sulfonylureas, the following interactions of the drug Duglimax® with other medicinal products must be considered.
This drug is metabolized by cytochrome P450 2C9 (CYP2C9), which should be taken into account in case of co-administration of CYP2C9 inducers (e.g., rifampicin) or inhibitors (e.g., fluconazole).
Medicinal products that potentiate the hypoglycemic effect.
Insulin and oral anti-diabetic products, non-steroidal anti-inflammatory drugs, ACE inhibitors, allopurinol, anabolic steroids, male sex hormones, chloramphenicol, coumarin anticoagulants, cyclophosphamide, disopyramide, fenfluramine, fenyramidol, fibrates, fluoxetine, guanethidine, isophosphamide, MAO inhibitors, miconazole, fluconazole, para-aminosalicylic acid, pentoxifylline (high dose parenteral), phenylbutazone, probenecid, quinolone antibiotics, salicylates, sulfinpyrazone, sulfonamides, clarithromycin, tetracyclines, tritoqualine, trofosfamide, azapropazone, oxyphenbutazone, sympatholytics.
Medicinal products that weaken the hypoglycemic effect.
Acetazolamide, barbiturates, corticosteroids, diazoxide, diuretics, epinephrine (adrenaline) or sympathomimetics, glucagon, laxatives (long-term use), nicotinic acid (high doses), estrogens,

progestogens, oral contraceptives, phenothiazines, phenytoin, rifampicin, thyroid hormones, chlorpromazine, isoniazid.
Medicinal products that can both potentiate and weaken the hypoglycemic effect.
H_2 antagonists, clonidine and reserpine.
Blockers of β-adrenoreceptors reduce glucose tolerance. This may change metabolic control in diabetic patients. β-adrenoreceptor blockers may increase the risk of hypoglycemia (due to failure of counter-regulation).
Drugs reducing or blocking the signs of adrenergic counter-regulation of hypoglycemia.
Sympatholytics (β-adrenoreceptor blockers, clonidine, guanethidine, and reserpine).
Both acute and chronic alcohol intake may potentiate or weaken the hypoglycemic action of the drug Duglimax®.
This drug may either potentiate or weaken the effects of coumarin anticoagulants.
Bile acid sequestrants: colesevelam binds to glimepiride and reduces glimepiride absorption from the gastrointestinal 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.
Lactic acidosis may occur upon concomitant administration of some drugs. Patients should be closely monitored in case of concomitant administration of the following drugs: iodinated contrast agents, antibiotics with severe nephrotoxicity (gentamicin, etc.).
The hypoglycemic action upon co-administration with some medicinal products may be potentiated or weakened. The blood glucose levels and patient's condition should be closely monitored in case of co-administration with:
- drugs potentiating the hypoglycemic action: insulin, sulfonamides, sulfonylurea products, meglitinides (repaglinide, etc.), alpha-glycosidase inhibitors (acarbose, etc.), anabolic steroids, guanethidine, salicylates (aspirin, etc.), β-blockers (propranolol, etc.), MAO inhibitors, angiotensin converting enzyme inhibitors;
- drugs weakening the hypoglycemic action: adrenaline, sympathomimetics, corticosteroids, thyroid hormones, estradiol, estrogens, oral contraceptives, thiazide and other diuretics, pyrazinamide, isoniazid, nicotinic acid, phenothiazines, phenytoin, calcium channel blockers, β-2-agonists such as salbutamol, formoterol, etc.)
Glyburide: in a single-dose interaction study in type II diabetes subjects, co-administration of metformin and glyburide did not result in any changes in either pharmacokinetics or pharmacodynamics of metformin. Decreases in the area under the "concentration/time" curve (AUC) and maximum plasma concentration (C_{max}) of glyburide were observed but were highly variable. The single-dose nature of this study and the lack of correlation between metformin blood levels and its pharmacodynamic effects makes the clinical significance of this interaction uncertain.
Furosemide: a single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma concentration and blood C_{max} by 22 % and blood AUC by 15 %, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} 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 study of metformin and nifedipine interaction in healthy volunteers demonstrated that co-administration of nifedipine increased the C_{max} and AUC of metformin by 20 % and 9 %, respectively, and increased the amount of the drug excreted in the urine. The time to maximum plasma concentration (T_{max}) and half-life of metformin were unaffected. Nifedipine was shown to enhance the absorption of metformin. Metformin had minimal effects on nifedipine pharmacokinetics.
- medicinal products that may affect renal function may result in hemodynamic changes, or cationic medicinal products eliminated by renal tubular secretion.

Cationic drugs: cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in healthy volunteers in both single-and multiple-dose metformin and cimetidine drug interaction studies. These studies demonstrated a 60 % increase in metformin C_{max} and total blood concentrations and a 40 % increase in plasma and blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretically possible (except for cimetidine), careful patient monitoring and dose adjustment of metformin and (or) the interacting drug is recommended in patients taking cationic medications that are excreted via the proximal renal tubular secretory system.
Other. In healthy volunteers, the pharmacokinetics of metformin and propranolol, as well as metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.
The plasma protein binding of metformin is negligible. Therefore, it is less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to sulfonylureas, which are extensively bound to plasma proteins.
Metformin may decrease the anticoagulant action of phenprocoumon. Close monitoring of INR (international normalized ratio) is therefore advised.
Levothyroxine may decrease the hypoglycemic action of metformin. Blood glucose levels should therefore be monitored, especially upon initiation or discontinuation of thyroid hormones, and the dose of metformin adjusted, if necessary.
Organic cation transporters (OCT).
Metformin is a substrate of both transporters OCT1 and OCT2.
Co-administration of metformin with
• OCT1 inhibitors (such as verapamil) may reduce the efficacy of metformin.
• OCT1 inducers (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
• OCT2 inhibitors (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentrations.
• Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter the efficacy and renal elimination of metformin.
Caution is therefore advised when co-administering these drugs with metformin, especially in patients with renal impairment, as metformin plasma concentrations may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Administration details.
Special precautions
Careful monitoring of the patient's condition is required during the first week of treatment because of increased risk of hypoglycemia. The following patients or conditions are associated with a risk of hypoglycemia:
- unwillingness or incapacity of the patient to cooperate with the doctor (more commonly in elderly patients)
- undernutrition, irregular mealtimes, skipped meals;
- imbalance between physical exertion and carbohydrate intake, severe myokinesis;
- alcohol consumption;
- renal insufficiency (may lead to increased sensitivity to the hypoglycemic effect of glimepiride);
- overdosage with the drug;
- certain decompensated endocrine system disorders (e.g., disorders of thyroid function and anterior pituitary or adrenocortical insufficiency), which may affect carbohydrate metabolism or counter-regulation of hypoglycemia;

- concurrent administration of certain other medicinal products (see section “Interaction with other medicinal products and other forms of interaction”).

If such risk factors of hypoglycemia are present, the dosage of the drug Duglimax® or the entire therapy should be adjusted. This also applies whenever any illness occurs or the patient's lifestyle changes. Symptoms of hypoglycemia caused by adrenergic counterregulation may be milder or absent in cases where hypoglycemia develops gradually: in the elderly, in patients with autonomic neuropathy or those receiving concurrent treatment with sympatholytics.

General precautions

Hypoglycemia

It is known from other sulfonylureas that, despite the initial success of the countermeasures taken, hypoglycemia may recur. Patients must therefore remain under close observation. Possible symptoms of hypoglycemia include headache, ravenous hunger, nausea, vomiting, fatigue, apathy, insomnia, restlessness, sleep disturbances, aggressiveness, impaired concentration, impaired alertness and reaction, depression, confusion, speech disorders, aphasia, visual disorders, tremor, pareses, sensory disturbances, dizziness, loss of self-control, delirium, convulsions of central origin, loss of consciousness, coma, somnolence, shallow respiration and bradycardia. In addition, signs of adrenergic counter-regulation may be present: excessive 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. Patients with severe hypoglycemia further require immediate treatment and follow-up by a physician, and, in some circumstances, hospitalization. Hypoglycemia can be nearly always promptly controlled by immediate intake of carbohydrates (glucose or sugar, e.g., lump sugar, fruit juice containing sugar, sweetened tea including sugar). Patients should carry at least 20 g of sugar for such cases. Patients as well as their family should be informed on hypoglycemia risks, symptoms, methods of treatment and risk factors. Help from others may be necessary to avoid complications. Artificial sweeteners are ineffective in controlling blood glucose.

Lactic acidosis.

Lactic acidosis is a rare but serious metabolic complication that can occur due to metformin accumulation during treatment with this drug. When it occurs, it is fatal in approximately 50 % of cases. Lactic acidosis may also occur in association with certain pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxia. Lactic acidosis is characterized by elevated blood lactate levels (≥ 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma of over 5 μg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patients per year, with approximately 0.015 fatal cases/1000 patients per year). The reported cases occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical pathologies and multiple concomitant medications.

The risk of lactic acidosis increases proportionally to the severity of renal dysfunction and the patient's age. However, the risk of lactic acidosis in patients taking metformin can be significantly reduced by continuous monitoring of kidney function and using the minimum effective doses of metformin.

In addition, this drug should be immediately discontinued in the presence of any conditions accompanied by hypoxemia, dehydration, or septicemia.

Because impaired hepatic function may significantly limit the ability to clear lactate, this drug should be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol consumption (both acute and chronic) during administration of this drug, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, the drug should be temporarily withheld before performing any studies with intravascular administration of contrast media and before any surgical intervention.

The onset of lactic acidosis is often subtle and is accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increased somnolence, and nonspecific abdominal discomfort. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible significance of such symptoms. The patient should therefore be instructed to notify the physician immediately if such symptoms occur.
Examination of such parameters as plasma electrolytes and ketones, blood glucose, blood pH, blood lactate and metformin levels may also be useful. Once the patient is stabilized on any dose of the drug Duglimax®, gastrointestinal symptoms which are common upon initiation of therapy with metformin are unlikely to be drug-related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking this drug do not necessarily indicate impending lactic acidosis. It may be explained by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in when performing blood tests.
Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketouria and ketonemia).
Lactic acidosis is a medical emergency that must be treated in a hospital setting. In patients with lactic acidosis receiving Duglimax®, the drug should be discontinued immediately, and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery from lactic acidosis.
- Optimal blood glucose levels should be maintained simultaneously by diet and adequate exercise, and, if necessary, by weight loss as well as by regular administration of this drug. Clinical signs of poorly controlled blood glucose levels include oliguria, thirst, polydipsia, and dry skin.
- Upon initiation of administration, patients should be informed about the benefits and potential risks associated with the use of this drug, as well as about the importance of following a diet and regular exercise. The importance of the patient’s positive cooperation with the medical staff should also be emphasized.
- Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of bringing these levels toward the normal range. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term glycemic control.
- If a patient receives a treatment prescribed by another physician (e.g., upon hospitalization, accident, need for medical attention on holidays), the patient should inform them of one’s current diabetes control situation and previous medication.
- In exceptional stress situations (e.g., trauma, surgery, infectious diseases with high fever), blood glucose regulation may deteriorate, and a temporary change over to insulin may be necessary to maintain good metabolic control.
- Treatment should be started at the lowest dosage. Regular monitoring of glucose levels in blood and urine is required during treatment with this drug. In addition, determination of glycosylated hemoglobin is recommended. The effectiveness of therapy should be assessed and, if not satisfactory, a switch to another therapy should be promptly made.
- Alertness and reactions may be impaired due to hypo- or hyperglycemia, especially when initiating treatment, when switching to another medicinal product or when this drug is not taken regularly. This may affect the ability to drive or to operate other mechanisms.
- Monitoring of renal function: metformin is known to be mostly excreted by the kidneys, therefore the risk of metformin accumulation and lactic acidosis increases in proportion to the degree of renal impairment. Thus, patients with plasma creatinine levels above the upper limit of normal for their age should not receive this drug. Elderly patients require careful dose titration of the drug Duglimax® to establish the minimum dose providing adequate glycemic effect since the renal function deteriorates

with age. Regular assessment of renal function is required in elderly patients, and this drug should not normally be titrated to the maximum dose.
Renal function should be assessed and confirmed to be normal prior to initiation of treatment and not less than once a year following initiation of treatment with this drug. Renal function should be assessed more frequently in patients expected to develop renal dysfunction, and the drug should be discontinued if signs of dysfunction are detected.
- Use of concomitant medications that may negatively affect renal function or metformin pharmacokinetics: concomitant use of medicinal products that may negatively affect renal function or result in significant hemodynamic change, or may interfere with the pharmacokinetics of this drug, such as cationic drugs, should be used with caution as they are eliminated by renal tubular secretion. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or during diuretic therapy or therapy with nonsteroidal anti-inflammatory drugs.
- This medicinal product should be prescribed only in patients diagnosed with diabetes mellitus. These should be distinguished from patients with diseases accompanied by diabetes-like symptoms (renal glycosuria, age-related glucose metabolism disorders, thyroid dysfunction) including glucose intolerance or glycosuria.
- Drug dose adjustment: in some patients, oral antidiabetics may need to be discontinued or their dose reduction may be required. The effectiveness of oral antidiabetic drugs decreases in many patients over time due to progression of the underlying disease or complication of infection. Therefore, the decision regarding the continuation of therapy with this medicinal product, selection of the dosage and concurrent administration of other drugs should be based on such factors as food intake, body weight change, blood glucose levels, infection, etc.
- Hypoxic states: cardiovascular collapse (shock) of any origin, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. If such states occur in patients receiving Duglimax®, the drug should be immediately discontinued.
- Alcohol intake: alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should therefore be warned against excessive alcohol intake, acute or chronic, while receiving the drug Duglimax®.
- Vitamin B_{12} levels: a decrease to subnormal plasma vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7 % of patients receiving metformin in controlled clinical trials lasting 29 weeks. The risk of low vitamin B_{12} levels increases with the increase in the metformin dose, duration of treatment and/or presence of risk factors known to cause vitamin B_{12} deficiency. The mechanism of this phenomenon is currently known to be multifactorial, however, it is very rarely accompanied by anemia and is rapidly reversible with discontinuation of this drug or vitamin B_{12} supplementation.
In case of suspicion of vitamin B_{12} deficiency (such as anemia or neuropathy), vitamin B_{12} serum levels should be monitored. Certain individuals appear to be predisposed to developing subnormal vitamin B_{12} levels. Periodic vitamin B_{12} monitoring may be necessary in patients with risk factors for vitamin B_{12} deficiency.
Metformin therapy should be continued for as long as it is tolerated and is not contraindicated, and appropriate corrective treatment for vitamin B_{12} deficiency provided in line with current clinical guidelines.
- Change in the clinical status of patients with previously controlled diabetes mellitus: a diabetic patient previously well controlled on metformin tablets who develops laboratory abnormalities or clinical illness (in particular fatigue, poorly defined illness) should be promptly evaluated for evidence of ketoacidosis or lactic acidosis. Evaluation should include plasma electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, treatment with the drug Duglimax® must be discontinued immediately and other appropriate corrective measures initiated.

- Loss of control of blood glucose: when a patient stabilized on any treatment regimen is exposed to stress such as fever, tremor, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold this drug and temporarily administer insulin. Should secondary failure occur during treatment with the drug, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.
- Patients with specific work conditions: for patients who work at high altitudes or drive a car, the drug should be prescribed with caution, as lactic acidosis or severe delayed hypoglycemia may occur. Such patients and their families should be fully informed of the risk of developing lactic acidosis or hypoglycemia and exercise great caution. Patients should be informed of the safety, efficacy and alternative treatments. In addition, they should be informed of the importance of regular food intake and adherence to dietary instructions, regular physical exercise, and regular testing of blood glucose, glycated hemoglobin, renal function, and hematologic parameters. Obese patients should follow a low-calorie diet.
The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the "Special precautions" and "General precautions" sections should be explained to patients. Patients should be advised to discontinue this drug immediately and to promptly consult their physician if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific unexplained symptoms occur. Once a patient is stabilized on any dose of this drug, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug-related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.
A physician should explain the patient and the family about the risks, symptoms and occurrence conditions of hypoglycemia.
Patients should be counseled against excessive alcohol intake, either acute or chronic, during treatment with the drug Duglimax®.
- Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be exercised in patients with G6PD deficiency, and a non-sulfonylurea alternative should be considered.
Increased risk of cardiovascular mortality.
The administration of antidiabetic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet in combination with insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP) to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes mellitus. UGDP reported that in patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 g/day) or diet plus a fixed dose of phenformin (100 mg/day), the cardiovascular mortality rate was approximately 2.5 times greater than that in patients treated with diet alone, which led to discontinuation of treatments in both cases during the UGDP study. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and benefits of using metformin and of alternative modes of therapy. Although only one drug in the sulfonylurea class (tolbutamide) and one drug in the biguanide class (phenformin) were included in this study, it is reasonable from a safety standpoint to consider that this warning may also apply to other respective anti-diabetic drugs, in view of their close similarities in the mode of action and chemical structure.
Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism.
Elderly patients.
Metformin and glimepiride are known to be mostly excreted by the kidneys. Because the risk of serious adverse reactions to Duglimax® is greater in patients with impaired renal function, it should only be used in patients with normal renal function. Due to the fact that renal function decreases with age, in elderly patients, metformin should be used with caution with regard to renal function and regular monitoring of renal function should be performed when necessary.

Use in children.
The safety and effectiveness of the drug in children (under 18 years of age) have not been established. Studies of administering the drug in maturity-onset diabetes of the young (MODY) have not been conducted.
Metformin monotherapy
Prior to initiation of metformin treatment, it should be confirmed whether the patient has type II diabetes mellitus. Although it was confirmed that metformin monotherapy did not negatively affect growth and sexual maturation of patients, no long-term study results are as of now available for these specific points. Therefore, it is recommended that the impact of metformin on these parameters be carefully monitored when this drug is administered to children, in particular those before puberty.
Only 15 patients aged 10 to 12 participated in a controlled clinical trial of metformin in children and adolescents in the growth phase. Although the efficacy and safety of metformin in children under 12 years of age did not differ from those in children over 12 years of age, caution should be exercised when prescribing metformin to children aged 10 to 12.
Other effects
Impact on body weight. Compared to other commonly used glucose-lowering medications (sulfonylureas, thiazolinediones, etc.), the drug Duglimax® presents more benefits as it does not lead to weight gain in patients with type II diabetes mellitus. Steady or reduced body weight resulting from the use of this drug limits other risk factors associated with weight gain. Stabilization or reduction of body weight with this drug limits the adverse effects of other risk factors associated with weight gain. More stable glycemic control and reduced risks of complications of diabetes can be obtained from a prolonged use of this drug.
Drug abuse and dependence. Metformin hydrochloride possesses no primary or secondary pharmacodynamic properties which could result in its abuse as a recreational drug or in development of addiction.
Laboratory tests.
Periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (plasma creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if it is suspected, the possibility of vitamin B_{12} deficiency should be ruled out.
If a patient has intolerance to some sugars, it is necessary to consult a physician before taking this medication because the product contains lactose.

Use during pregnancy and breastfeeding.
Duglimax® must not be taken during pregnancy due to the existing risk of teratogenicity. Pregnant patients and patients planning a pregnancy must inform their physician in order to reduce the risk of fetal congenital anomaly caused by abnormal blood glucose levels. If possible, such patients should be changed over to insulin to maintain the blood glucose levels within a normal range.
The drug should not be taken by breastfeeding women to avoid glimepiride and metformin passing into the child's organism with breast milk. If necessary, the patient must use insulin or must stop breastfeeding.
Carcinogenicity, mutagenicity, impairment of fertility
Glimepiride
- Studies in rats at doses of glimepiride of up to 5,000 ppm (which is approximately 340 times the maximum recommended human dose, based on surface area) under adequate nutrition for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation. This effect is dose related and is thought to be the result of chronic pancreatic stimulation. The No Observable Effect Level (NOEL) for adenoma formation in mice in this study was 320 ppm under adequate nutrition, or 46−54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose (8 mg once daily) based on surface area.

- Glimepiride did not demonstrate mutagenic effects in *in vitro* and *in vivo* mutagenicity studies.
- There was no effect of glimepiride on male mouse fertility in animals exposed to up to 2,500 mg/kg body weight (>1,700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4,000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

Metformin

- Long-term carcinogenicity studies of metformin have been performed in rats and mice with a dosing duration of 104 weeks and 91 weeks, respectively. Doses up to 900mg/kg/day and 1500 mg/kg/day, respectively, were used. These doses were both approximately three times the maximum recommended human daily dose based on body surface area. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day.
- No evidence of a mutagenic potential of metformin was found in either of the following tests: the Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), chromosomal aberration test (human lymphocytes), or *in vivo* micronucleus assay (mouse bone marrow).
- Fertility of male or female rats was unaffected by metformin administration at doses up to 600 mg/kg/day, that is, at doses approximately twice the maximum recommended human daily dose based on body surface area.

Effect on reaction rate when driving motor transport or using other mechanisms.

Patients should be warned about the need to exercise caution when driving motor transport and operating mechanisms.

Dosage and administration.

The dose of antidiabetic drugs should be selected individually, considering the patient's blood glucose levels.

Generally, it is recommended to initiate treatment at the lowest effective dose and increase the dose depending on the patient's current medication and blood glucose levels. Regular monitoring of blood glucose levels should be performed for this.

For patients whose diabetes is not controlled by monotherapy with sulfonylureas or metformin: the usual starting dose of this drug is 1 mg/500 mg, which should be administered once daily and can be adjusted depending on the concomitant therapy with another hypoglycemic medication or according to the patient's glycemia levels. When switching from sulfonylureas with a prolonged half-life (e.g. chlorpropamide), the patient should be closely monitored for hypoglycemia, as hypoglycemia may develop as a result of the additive effect of the drugs.

Although glimepiride monotherapy generally had minimal additional effects when dosed at 4 mg or more daily, some patients showed improved metabolic control when the dose was increased to 6 mg (or 8 mg).

The drug is used exclusively in adult patients.

This drug should be administered once or twice daily immediately before or with the meals.

When switching from combination therapy to individual tableted medication: in case of switching from combination therapy with glimepiride and metformin in the form of separate tablets, Duglimax® should be administered based on the dosage and administration method of glimepiride and metformin hydrochloride that are being currently administered.

If necessary, the dose can be increased to the highest recommended daily dose of 8 mg of glimepiride and 2000 mg of metformin, considering the therapy currently used, effectiveness or tolerability of the drug. Therefore, careful blood glucose monitoring is required.

Never take a higher dose of the drug to try to make up for a missed dose.

Patients should be informed that the drug should be swallowed whole without crushing and chewing, as it has sustained-release properties.

Children.
The safety and effectiveness of using the drug in children have not been established. Studies in maturity-onset non-insulin-dependent diabetes mellitus of the young (MODY) have not been conducted.

Overdose.
Since this drug contains glimepiride, overdose can lead to a decrease of blood glucose levels. As soon as overdose of glimepiride has been discovered, a physician must be notified immediately. The patient must immediately take sugar, preferably in the form of glucose, unless a physician has already undertaken responsibility for treating the overdose. Mild hypoglycemia without loss of consciousness or neurological disorders should be treated aggressively with oral glucose and adjustments in drug dosage and/or diet. Close monitoring of the patient should be continued until the physician is assured that the patient is out of danger. Treatment primarily consists in preventing absorption of the drug by inducing vomiting and then drinking sugary soft drinks or water containing activated charcoal (adsorbent) and sodium-sulphate (laxative). If large quantities of the drug have been absorbed, gastric lavage should be conducted, and then activated charcoal and sodium-sulphate should be taken.
Significant overdoses and severe reactions with signs such as loss of consciousness or other serious neurological disorders are medical emergencies and require immediate treatment and admission to hospital. If hypoglycemic coma is diagnosed or suspected due to serious overdose, the patient should be given a rapid intravenous injection of concentrated (50 %) glucose solution or 40 ml of 20 % glucose solution followed by a continuous infusion of a more diluted (10 %) glucose solution at a rate that maintains blood glucose at a level above 100 mg/dL.
Alternatively, administration of glucagon i.v., i.m., or s.c. may be prescribed in adults, for example, in doses of 0.5 to 1 mg intravenously, subcutaneously or intramuscularly. The patient should be closely monitored for at least 24-28 hours, because hypoglycemia may recur after apparent clinical recovery.
In particular, when treating hypoglycemia due to accidental intake of glimepiride in infants and young children, the dose of glucose given must be carefully adjusted and the blood glucose level should be continuously monitored.
Because this drug contains metformin, lactic acidosis may occur. Hypoglycemia has not been observed when metformin hydrochloride was ingested in doses of up to 85 mg. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis is the most effective treatment for removal of accumulated drug in patients with suspected metformin overdosage.
Pancreatitis may occur as a result of metformin overdose.

Adverse reactions.
Lactic acidosis: see section “Administration details”.
Hypoglycemia: see section “Administration details”.
Gastrointestinal disorders: gastrointestinal symptoms, including diarrhea, nausea, vomiting, abdominal bloating, dyspepsia, constipation, abdominal pain and anorexia are the most common reactions to this drug and are approximately 30 % more frequent in patients on metformin therapy than in placebo-treated patients, particularly during initiation of therapy with this drug. These symptoms are generally transient and resolve spontaneously during continued therapy. Occasionally, temporary dose reduction may be useful. In clinical trials, metformin had to be discontinued due to gastrointestinal reactions in approximately 4 % of patients.
Because gastrointestinal symptoms upon initiation of treatment appear to be dose-related, they may be decreased by gradual dose escalation by taking the drug with meals. Because significant diarrhea and/or vomiting can cause dehydration and extrarenal azotemia, the drug should be temporarily discontinued under such circumstances.
For patients who have been stabilized on this drug, nonspecific gastrointestinal symptoms should not be attributed to therapy unless concomitant illness or lactic acidosis has been ruled out.

Glimepiride therapy may sometimes cause nausea, vomiting, sensations of bloating or pressure in the epigastrium, abdominal pain, and diarrhea.
Special senses: approximately 3 % of patients may complain on taste disturbance or metallic taste during initiation of the drug therapy, which usually resolves on its own. Due to the change in blood glucose levels, temporary visual impairment may occur, especially during initiation of therapy. In post-marketing experience, dysgeusia has occurred after administration of glimepiride (frequency not known).
Skin reactions and hypersensitivity: occasionally, allergic or pseudo-allergic reactions (for example, mild erythema (very rare − <0,01%), pruritus, urticaria, or rash) may occur. Most of these reactions are mild but may develop into serious reactions with dyspnea and a fall in blood pressure, sometimes progressing to shock. In the event of urticaria a physician must be notified immediately. Cross allergy reactions with sulfonylureas or sulfonamides or their derivatives may occur.
Hematological parameters: thrombocytopenia may occur rarely; in isolated cases, leukocytopenia, or hemolytic anemia, erythrocytopenia, granulocytopenia, agranulocytosis, pancytopenia may occur. Careful monitoring of the patient's condition is required, as cases of aplastic anemia have been reported with sulfonylureas. If these occur, the medication should be discontinued, and adequate treatment should be initiated. Cases of severe thrombocytopenia with a platelet count of <10000/µl and thrombocytopenic purpura have been reported (frequency not known). A decrease/deficiency of vitamin B_{12} levels is often observed during treatment with the drug. Patients taking metformin for prolonged periods of time have demonstrated decreased absorption of vitamin B_{12} and a decrease of its serum levels, though, this phenomenon is clinically insignificant (< 0,01%). However, cases of peripheral neuropathy in patients with vitamin B_{12} deficiency have been reported in post-marketing experience of using the drug (frequency not known). Plasma folic acid levels were not significantly decreased. Only megaloblastic anemia was reported during administration of the drug, the incidence of neuropathy was not increased. Close monitoring of serum vitamin B_{12} or periodic parenteral supplementation of vitamin B_{12} are therefore required.
Hepatobiliary disorders: in some cases, elevation of liver enzymes and impairment of liver function (cholestasis and jaundice), as well as hepatitis which may progress to liver failure, may occur. During administration of metformin, liver function abnormalities and hepatitis were reported, which resolved upon discontinuation of metformin.
Other reactions: in some cases, allergic vasculitis, hypersensitivity of skin to light, or decrease in serum sodium concentrations may be observed.
Additionally, other adverse reactions with unknown frequency occurred:
- reduction of thyroid-stimulating hormone levels in patients with hypothyroidism;
- hypomagnesemia resulting from diarrhea;
- encephalopathy;
- alopecia, weight gain (after glimepiride administration).

Adverse reactions in children with metformin monotherapy. Adverse reactions observed in a clinical trial of a small-size cohort comprised of children aged 10 to 16 treated with metformin for 1 year, as well as adverse reactions published and reported during post-marketing surveillance were similar in terms of characteristics and severity to those reported in adults.
Adverse reactions based on the results of post-marketing surveillance.
The frequency of adverse reactions, regardless of the cause-effect relationship to the studied drug therapy, in a 6-year post-marketing surveillance study for drug re-examination in 1235 patients with non-insulin-dependent diabetes mellitus (type II) was 2,75 % (34/1235 patients, 35 cases). These adverse reactions included: hypoglycemia in 0,8 % (10/1235 patients, 10 cases); abdominal pain in 0,57 % (7/1235 patients, 7 cases); abdominal bloating – 0,49 % (6/1235 patients, 6 cases); vomiting and dyspepsia in 0,16 % each reaction (2/1235 patients, 2 cases); prostate hypertrophy, heart palpitations, dizziness, diarrhea, nausea, leg edema, cardiac arrest, and rectal cancer in 0,08 % each reaction (1/1235 patients, 1 case). The frequency of adverse drug reactions where the cause-effect relationship to the studied drug therapy could not be ruled out was 2,02 % (25/1235 patients, 26 cases),

including: hypoglycemia in 0,8 % (10/1235 patients, 10 cases); abdominal bloating and abdominal pain in 0,48 % each reaction (6/1235 patients, 6 cases); heart palpitations, vomiting, dyspepsia and dizziness in 0,08 % each reaction (1/1235 patients, 1 case). Serious adverse reactions included cardiac arrest, and rectal cancer in 0,08 % each reaction (1/1235 patients, 1 case), neither of which had the cause-effect relationship to the studied drug therapy. Unexpected adverse reactions included dyspepsia in 0,16 % (2/1235 patients, 2 cases); prostate hypertrophy, leg edema and rectal cancer in 0,08 % each reaction (1/1235 patients, 1 case). Of these, dyspepsia was an adverse drug reaction where a causal relationship to this drug could not be ruled out.

Adverse reactions with glimepiride (for oral administration) monotherapy based on the results of post-marketing surveillance.

The incidence of adverse reactions, regardless of the cause-effect relationship to the studied drug therapy, in a 6-year post-marketing surveillance study in 12 056 patients was 1,2 % (149/12 056 patients, 181 cases). Hypoglycemia, with an incidence of 0,75 % (90/12 056 patients, 102 cases). was the most common adverse reaction; in order of decreasing incidence, it was followed by vertigo (dizziness) – 0,08 % (10/12 056 patients, 10 cases); liver dysfunction – 0,07 % (8/12 056 patients, 8 cases), and abdominal pain – 0,06 % (7/12 056 patients, 7 cases). Of these, newly reported adverse reactions that had not been identified in pre-registration clinical trials were arthralgia, dyspepsia, facial edema (2 cases each), impotence, alopecia, hyperemia, and gastritis (1 case each).

If any of the above-mentioned adverse reactions, other undesired reactions, or unexpected changes occur, patients should immediately consult their doctor. Certain adverse reactions including severe hypoglycemia, special hematologic changes, severe allergic or pseudo-allergic reactions, and hepatic insufficiency may be life-threatening under certain conditions. Therefore, patients should immediately inform their doctor about such reactions and discontinue the drug until the doctor's instructions are received.

Reporting of suspected adverse reactions.

Reporting adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the Automated pharmacovigilance information system available at: https://aisf.dec.gov.ua.

Shelf-life.

2 years.

Storage conditions.

Store in the original package at a temperature not more than 25 °C.
Keep out of reach of children.

Package.

15 tablets are in a blister; 2 or 4 blisters are in a carton box.

Conditions of supply.

By prescription.

Manufacturer.

LLC "KUSUM PHARM".

Address of manufacturer and manufacturing site.

40020, Ukraine, Sumy region, Sumy, Skryabina Str. 54.

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