1. **Trade name of The Medicinal Product** :

Kayglim

2. **Quantitative and Qualitative Composition**:
Glimepiride 2 mg, Metformin hydrochloride - 500 mg

3. Pharmaceutical form

Film coated tablet

4. **Clinical Particulars**

4.1 **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 glimepiride monotherapy.

4.2 Posology and Method of Administration.

Typically the dose of medicine **Kayglim** 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 **Kayglim**, 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 **Kayglim** 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. In order to avoid development of hypoglycemia, the dose should be promptly reduced or administration should be stopped.

Kayglim 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 should not exceed daily dose of glimepiride and metformin already being taken by a patient in order to avoid hypoglycemia.

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.

4.3 Contraindications –

Diabetes mellitus type 1; - Diabetic ketoacidosis including history of diabetic coma and precoma, acute or chronic metabolic acidosis; - Increased sensitivity to sulfonylureas, sulfonamides or biguanides, as well as any of the excipients of the medicine; - Severe hepatic dysfunction (lack of experience of administration; in order to provide adequate glycemic control, such patients should be treated with insulin).

4.4 Precautions for Use and Special Warnings –

Particularly careful monitoring of the glucose concentration in the blood is required in the first weeks of treatment with Kayglim, because of the risk of hypoglycemia, especially in the following conditions, under which risk of hypoglycaemia is increased: - Unwillingness or inability of the patient to cooperate with the physician [most often this is shown in the elderly patients); - Lack of nutrition, regular food intake, omission of meals; - Incompliance between physical activity and carbohydrate intake; - Changes in diet; - Use of alcoholic beverage, especially in combination with omission of meals; - Liver and kidney insufficiency; - Certain uncompensated endocrine disorders such as thyroid disorders, lack of hormones of the anterior pituitary or the adrenal cortex, affecting carbohydrate metabolism or activation of mechanisms aimed at increase of glucose concentration in the blood during hypoglycemia; - Treatment with glimepiride in the absence of any indication; - Over-dosage of glimepiride; - Development of intercurrent disease during treatment or lifestyle changes; In these cases, more careful control of blood glucose concentrations and hypoglycemia symptoms is required, dose

adjustment of **Kayglim** or the entire hypoglycemic therapy may become necessary."), Elderly patients (in these cases asymptomatic decrease in kidney function is often observed); - In the situations where renal function may deteriorate, such as starting of administration of antihypertensive medicines or diuretics, as well as non-steroid anti-inflammatory drugs (NSAIDs) by a patient (increased risk of lactic acidosis and other side effects of metformin); - When performing heavy physical exercise (risk of development of lactic acidosis while taking metformin is increased); - In case of lack of symptoms of adrenergic anti-hypoglycemic regulation in response to developing hypoglycemia (in elderly patients, with autonomic neuropathy or simultaneous therapy with beta-blockers, clonidine, guanethidine, reserpine and other sympatholitics) (more careful monitoring of blood glucose concentrations is required in these patients); - In case of insufficiency of glucose-6-phosphate dehydrogenase (when receiving sulfonylureas, hemolytic anemia may develop in these patients, therefore administration of alternative hypoglycemic drugs, non-sulfonylurea, should be considered).

4.5 Interactions Interaction of glimepiride with other pharmaceutical products

Adverse reactions may develop in case of simultaneous administration of glimepiride with other pharmaceutical products: enhancement or reduction of its hypoglycemic action. Based on clinical experience with glimepiride and other sulphonylureas, the following drug interactions should be considered. - With the pharmaceutical products that are inducers and inhibitors of isoenzyme SYR2S9: Glimepiride is metabolized via the cytochrome P450 2C9 (isoenzyme SYR2S9). In case of its simultaneous application with inductors of isoenzyme SYR2S9 (e.g. Rifampicin), hypoglycemic effects of glimepiride may decrease, while the abolition of inductors of isoenzyme SYR2S9 without dose adjustment of glimepiride may increase the risk of hypoglycemia. Simultaneous administration of inhibitors of isoenzyme SYR2S9 (e.g. Fluconazole) increases the risk of hypoglycemia and side effects of glimepiride, while the abolition of inhibitors of isoenzyme SYR2S9 without dose adjustment of glimepiride may reduce its hypoglycemic effect. - With the pharmaceutical products reinforcing hypoglycemic effect of glimepiride: insulin and insulin analogs, hypoglycemic agents for oral administration, angiotensin converting enzyme (ACE) inhibitors, anabolic steroids, male sex hormones, chloramphenicol, indirect anticoagulants, coumarin derivatives, cyclophosphamide, disopyramide, fenfluramine, feniramidol, fibrates, fluoxetine, guanethidine, ifosfamide, monoamine oxidase inhibitors (MAO), miconazole, fluconazole, aminosalicylic acid, pentoxifylline (high dose parenteral), phenylbutazone, azapropazone, oxyphenbutazone, probenecid, antimicrobials - quinolone derivatives, salicylates, sulfinpyrazone, clarithromycin, sulfanilamide antimicrobials, tetracyclines, tritokvalin, trofosfamide. Increased risk of hypoglycemia in case of simultaneous administration of these drugs with glimepiride and the risk of deterioration of glycemic control at their cancellation without correction of dose of glimepiride - With the pharmaceutical products that weaken the hypoglycemic action: acetazolamide, barbiturates, glucocorticosteroids, diazoxide, diuretics, epinephrine (adrenaline) or other sympathomimetics, glucagon, laxatives (prolonged use), nicotinic acid (high dose), estrogens, progestogens, phenothiazines, phenytoin, rifampicin, thyroid hormone drugs. The risk of weakening the hypoglycemic action of glimepiride in case of concomitant administration with these medicines and increased risk of development of hypoglycemia in case of abolition without correction dose of glimepiride - With H2-histamine receptor blockers, beta-blockers, clonidine, reserpine, guanethidine Perhaps either increase or decrease of hypoglycemic effects of glimepiride. Careful monitoring of blood glucose levels shall be necessary. - With beta-blockers, clonidine, guanethidine and reserpine Beta-blockers, clonidine, guanethidine and reserpine may reduce or completely eliminate the reactions of the adrenergic counter-regulation (reactions of the sympathetic nervous system as a response to hypoglycemia, aimed at increase of blood glucose concentration), which results in a weakening of manifestation of hypoglycemia (makes its development more invisible to the patient and doctor) and therefore makes its early detection and treatment difficult.

Interaction of metformin with other pharmaceutical products Unacceptable combination - With ethanol the risk of lactic acidosis increases in case of acute alcohol intoxication, particularly in case of missing or insufficient food intake, presence of liver failure. Avoid drinking of alcohol (ethanol) and ethanol-containing medicines. With antibiotics, having expressed nephrotoxic effect (gentamicin) Increased risk of development of lactic acidosis Combination with metformin, requiring caution . With Corticosteroids (for systemic or local administration), beta2-stimulators and diuretics, owing hyperglycemic activity The patient should be informed about the need for more frequent monitoring of blood glucose concentration, especially at the beginning of the combined therapy. You may need a dose adjustment of hypoglycemic medicines during administration or after discontinuation of the above-mentioned medicines. - With antihypertensive pharmaceutical products Antihypertensive pharmaceutical products, including ACE inhibitors, can change the blood glucose concentration. If necessary, the dose of metformin should be adjusted. Note, however, that hypoglycemia was not observed in case of administration of metformin in monotherapy in combination with ACE inhibitors. - With phenprokoumon Metformin may reduce the anticoagulant effect of phenprokoumon. Therefore, careful monitoring of international normalized ratio (INR) is recommended. - With levothyroxine sodium Levothyroxine sodium may reduce the hypoglycemic effect of metformin. We recommend monitoring of blood glucose concentration, especially at the

beginning of treatment or discontinuation of treatment of thyroid hormone, if necessary, metformin dose should be adjusted

4.6 Pregnancy and Breast-Feeding Pregnancy

Administration of the drug **Kayglim** is contraindicated during pregnancy because of the possible adverse effects on intrauterine fetal development. Pregnant women and women planning pregnancy should notify the doctor about this. During pregnancy and when planning, women with impaired glucose metabolism, which cannot be corrected with diet and physical activity, must receive insulin therapy in order to maintain normal blood concentrations of blood glucose level. Breast-feeding In order to avoid transfer of medicine to the child's body through breast milk, women should not take this medicine in breastfeeding period. In case of need for hypoglycemic therapy, the patient must be transferred to the insulin treatment, otherwise she must discontinue breastfeeding.

4.7 Driving and Using Machines

Speed of reactions of patients may deteriorate as a result of hyperglycemia and hypoglycemia, especially at the beginning of treatment or after a change in treatment, or in case of irregular administration of medicine. This may affect the ability required for driving of vehicles and fulfillment of other potentially hazardous activities. The patients should be warned of the need to exercise caution when driving, especially in the case of tendency for hypoglycemia and/or reduction of severity of its precursors.

4.9 Overdose

Since **Kayglim** contains glimepiride, overdose (such as acute and chronic administration of the medicine in high doses) can cause severe, life-threatening hypoglycemia. As soon as glimepiride overdose is determined, you should immediately inform your doctor. Until medical assistance arrives, the patient should immediately take sugar, if possible, in the form of dextrose (glucose). It is necessary to conduct gastric lavage and give activated charcoal to the patients, who have taken a life-threatening amount of glimepiride. Sometimes, hospitalization is required as a preventive measure. Light hypoglycemia without loss of consciousness or neurological manifestations should be treated by oral administration of dextrose (glucose), correction dose of **Kayglim** and\or the patient's diet. Significant overdose and serious hypoglycemic reactions with the symptoms such as loss of consciousness or other serious neurological disorders are critical conditions, requiring immediate hospitalization. In case of unconscious state, the patient should be given concentrated solution of glucose (dextrose) intravenously, for example, for adults the dose starts with 40 ml of 20% glucose (dextrose). Glucagon administration, for example, at a dose of 0.5 to 1 mg intravenously, subcutaneously or intramuscularly, is considered as an alternative treatment for adult patients. After rapid administration of glucose, it is necessary to conduct glucose infusion at a low concentration as long as the doctor is sure that the threat of resumption of hypoglycemia has passed. Blood glucose concentrations should be carefully monitored for at least 24-48 hours, as hypoglycemia may recur after apparent clinical recovery. Risk of recurrence of hypoglycemia in severe cases with a prolonged course may persist for several days. In case of treatment of hypoglycemia in children with accidental administration of glimepiride, the dose of administered dextrose should be very carefully adjusted under the constant control of blood glucose concentration, due to potential development of dangerous hyperglycemia.

5. Pharmacological Properties

5.1 Pharmacodynamics

Kayglim is a combined hypoglycemic medicine, which is composed of glimepiride and metformin. Pharmacodynamics

Glimepiride, one of the active substances of Kayglim, is an oral hypoglycemic medicine - sulfonylureas of the III generation. Glimepiride stimulates secretion and release of insulin from the pancreas beta-cells (pancreatic effect), improves sensitivity of peripheral tissues (muscle and fat) to the action of endogenous insulin (extrapancreatic action). Effect on insulin secretion Sulfonylureas increase insulin secretion by closing the ATP-dependent potassium channels, located in the cytoplasmic membrane of pancreatic beta-cells. By closing the potassium channels, they cause depolarization of the beta-cells, thus facilitating opening of calcium channels and increasing of transmission of calcium into the cells. Glimepiride is bounded and unbounded from the protein of pancreatic beta cells at a high replacement rate of (mol. mass - 65 kD/SURX), which is associated with the ATP-dependent potassium channels, however it is different from the binding sites of conventional sulfonylureas (protein with mol. mass - 140 kD/SUR1). This process leads to release of insulin by exocytosis, and the amount of secreted insulin is significantly lesser than with sulfonylureas of II generation (e.g. glibenclamide). Minimum stimulating effect of glimepiride on insulin secretion is provided and there is a

lower risk of development of hypoglycemia. Extrapancreatic activity As with traditional sulfonylureas, but to a greater extent, glimepiride has pronounced extrapancreatic effects (reduction of insulin resistance, antiatherogenic, antiplatelet and antioxidant action). Utilization of glucose by peripheral tissues (fat and muscle) occurs via specific transporter proteins (GLUT1 and GLUT4), located in the cell membranes. Transportation of glucose in these tissues in diabetes mellitus type 2 is limited in rate of glucose utilization stage. Glimepiride very rapidly increases the number and activity of molecules, glucose transporter (GLUT1 and GLUT4), which leads to an increase in glucose uptake by peripheral tissues. Glimepiride has a weak inhibitory effect on ATP-sensitive potassium channels of cardiomyocytes. Upon administration of glimepiride, the ability of metabolic adaptation to myocardial ischemia is preserved

Pharmacodynamics of metformin

Metformin is a hypoglycemic medicine from the biguanide group. Its hypoglycemic effect is possible only under condition of preservation of insulin secretion (although reduced). Metformin has no effect on the beta-cells of the pancreas and does not increase secretion of insulin. Metformin at therapeutic doses do not cause hypoglycemia in humans. The mechanism of action of metformin is not yet completely learnt. It is assumed that metformin may potentiate the effects of insulin or that it can increase the effects of insulin receptors in peripheral areas. Metformin increases insulin sensitivity due to increase in the number of insulin receptors on cell surface membranes. Besides metformin inhibits gluconeogenesis in the liver, reduces formation of free fatty acids and fat oxidation, reduces the concentration of triglyceride (TG) and low-density lipoproteids (LDL) and very low-density lipoprotein (VLDL) in blood. Metformin slightly reduces appetite and decreases absorption of carbohydrates in the intestine. It improves blood fibrinolytic properties due to suppression of tissue plasminogen activator inhibitor.

5.2 Pharmacokinetics Pharmacokinetics

Glimepiride with multiple daily dose of 4 mg glimepiride, maximum serum concentration (Cmax) is achieved after about 2.5 hours and is 309 ng / ml; there is a linear relationship between dose and Cmax, as well as between the dose and AUC (area under plasma “concentration – time” curve). When administered, bioavailability of glimepiride is almost complete. Food intake has no significant effect on absorption, with the exception of a slight slow-down of the rate of absorption. Glimepiride is characterized by a very low distribution volume (approximately 8.8 liters), approximately equal to the albumin distribution volume, high plasma protein binding level (99%) and low clearance (about 48 ml/min). After a single oral administration of glimepiride, 58% of the dose is excreted by the kidneys (as metabolites) and 35% of the dose is excreted through the intestines. Half-life in case of plasma concentrations of glimepiride in plasma, corresponding to the multiple administration, is 5-8 hours. After administration of high dose, half-life increases slightly. In urine and faeces two inactive metabolites are revealed, resulting the metabolism in the liver, one of them is hydroxy derivative, and the other - carboxy derivative. After oral administration of glimepiride, terminal half-life of these metabolites is 3-5 hours and 5-6 hours, respectively. Glimepiride is excreted in breast milk and crosses the placental barrier. Glimepiride poorly crosses the blood-brain barrier. Comparison of single and multiple (2 times daily) administration of glimepiride did not reveal significant differences in the pharmacokinetic parameters and their variability between patients was insignificant. Significant accumulation of glimepiride was absent. Pharmacokinetic parameters of glimepiride are the same for patients of different genders and various ages. In patients with impaired renal function (low creatinine clearance) tended to increase clearance of glimepiride and decrease in its average concentrations in the blood serum, which is likely caused by a more rapid clearance of glimepiride due to its lower binding to plasma proteins.

Pharmacokinetics of metformin

Metformin is absorbed from the gastrointestinal tract adequately after oral administration. Absolute bioavailability is 50-60%. Cmax, composed of average 2 mg/ml, is reached after 2.5 hours. In case of simultaneous food intake, absorption of metformin is reduced and slowed down. Metformin is rapidly distributed into the tissue, practically does not bind to plasma proteins. It is metabolized to a very small extent and excreted by the kidneys. The clearance in healthy subjects is 440 ml/min (4 times greater than that of creatinine), indicating presence of active tubular secretion of metformin. Half-life of metformin is approximately 6.5 hours. There is a risk of metformin accumulation in case of renal insufficiency. Pharmacokinetics Kayglim with the fixed dose of glimepiride and metformin In case of administration of fixed dose of the combined drug Kayglim (tablet containing glimepiride 2 mg + metformin 500 mg), Cmax and AUC values correspond to bioequivalence criteria when compared to the same parameters in case of administration of the same combination as separate preparations (tablet of glimepiride 2 mg and metformin 500 mg).

6.1 Excipients Excipients:

Lactose monohydrate - 50 mg, Carboxymethyl starch sodium - 15 mg, Povidone K30 - 25 mg Microcrystalline cellulose - 50 mg, Crospovidone - 10 mg, Magnesium stearate - 5 mg; Film coating: Hypromellose - 9.4 mg, Macrogol-6000 - 1.7 mg, Titanium dioxide (E 171) - 1.7 mg, Carnauba wax - 0.2 mg.

6.2 Storage Store at temperatures not above 30 ° C.

6.3 Shelf-life 3 years. Do not use the medicine after the expiry date stated on the package.

6.4 Nature and contents of container

The tablets are available in ALU- ALU blister pack of 3x10.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

KAYHELT PHARMA LTD

2, NINKU LINK, SECRETARIAT JUNCTION, JOS