

**PACKAGE LEAFLET**  
**for medical use of a medicinal product**

**Tiara Trio®**

***Qualitative and quantitative composition:***

amlodipine, hydrochlorothiazide, valsartan;

1 tablet of 5 mg/12.5 mg/160 mg contains:

*active substances:* amlodipine besylate equivalent to 5 mg of amlodipine, 12.5 mg of hydrochlorothiazide, 160 mg valsartan;

*excipients:* microcrystalline cellulose, croscarmellose sodium, crospovidone, colloidal anhydrous silica, magnesium stearate, Opadray II 85 F pink;

1 tablet of 10 mg/12.5 mg/160 mg contains:

*active substances:* amlodipine besylate equivalent to 10 mg of amlodipine, 12.5 mg of hydrochlorothiazide, 160 mg of valsartan;

*excipients:* microcrystalline cellulose, croscarmellose sodium, crospovidone, colloidal anhydrous silica, magnesium stearate, Opadray II 85 F white.

**Pharmaceutical form.** Film-coated tablets.

*Basic physical and chemical properties:*

5 mg/12.5 mg/160 mg tablets: pink, round, biconvex, film-coated;

10 mg/12.5 mg/160 mg tablets: white, round, biconvex, film-coated;

**Pharmacotherapeutic group.** Angiotensin II receptor blockers, other combinations. Amlodipine, hydrochlorothiazide, valsartan. ATC Code C09D X01.

***Pharmacological properties.***

*Pharmacodynamic properties.*

Tiara Trio® consists of three antihypertensive compounds with various complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium channel blocker class, valsartan is from the angiotensin ii blocker class, and hydrochlorothiazide is from the thiazide diuretic class. The combination of these three ingredients has an additive antihypertensive effect.

*Amlodipine*

Amlodipine as a compound of Tiara Trio® inhibits the transmembrane entry of calcium ions into the heart muscle and vascular smooth muscles. The mechanism of the antihypertensive effect of amlodipine is due to a direct smooth muscle relaxant effect causing a decrease in peripheral vascular resistance and blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Myocardial and vascular smooth muscle contractility is dependent on the flux of extracellular calcium ions into the cells through specific ion channels.

After the administration of therapeutic doses of amlodipine to patients diagnosed with hypertension, amlodipine causes vasodilation, which results in a reduction of supine and standing blood pressure. During these blood pressure reductions, there are no clinically significant changes in heart rate or plasma catecholamine levels with long-term use.

Amlodipine plasma concentrations correlate with the effect in both young and elderly patients.

In patients with hypertension and normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and increase in glomerular filtration rate (GFR) and effective renal plasma flow, without a change in filtration fraction or proteinuria.

#### *Valsartan*

Valsartan is an active with oral administration, potent and specific angiotensin II receptor blocker. Valsartan acts selectively on the receptor subtype AT<sub>1</sub> which is responsible for the known actions of angiotensin II.

Administration of valsartan to patients with hypertension results in a drop of blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, the onset of antihypertensive activity occurs within 2 hours and the peak drop in blood pressure is achieved within 4 to 6 hours. The antihypertensive effect persists for 24 hours after administration. With repeated administration, the maximum reduction in blood pressure with any dose schedule is usually attained within 2 to 4 weeks.

#### *Hydrochlorothiazide*

The site of action of thiazide diuretics is primarily in the renal distal convoluted tubules. It has been shown that there are high-affinity receptors in the renal cortex which are the major binding site for the thiazide diuretics and inhibition of NaCl transport to the distal convoluted tubules. The mechanism of action of thiazides lies in inhibition of Na<sup>+</sup>Cl<sup>-</sup> transporters, perhaps by competing for the Cl<sup>-</sup> sites, thereby affecting electrolyte reabsorption mechanisms: they directly increase sodium and chloride excretion to an approximately equal extent and indirectly, as a result of the diuretic effect, reduce plasma volume with a consequent increase in plasma renin activity, aldosterone secretion and urinary potassium excretion, and due to a decrease in serum potassium.

#### Non-melanoma skin cancer (NMSC):

Based on epidemiological study results a cumulative dose-dependent relationship between hydrochlorothiazide administration and NMSC has been revealed. There are data on one study which included a population of 71,533 cases of basal cell carcinoma (BCC) and 8,629 cases of squamous cell carcinoma (SCC), and 1,430,833 and 172,462 cases in control population, respectively. Administration of high doses of hydrochlorothiazide (total dose  $\geq 50,000$  mg) resulted in the following adjusted odds ratio: 1.29 (95 % CI: 1.23–1.35) for BCC and 3.98 (95 % CI: 3.68–4.31) for SCC. There was a pronounced cumulative dose-effect relationship in cases of BCC and SCC. Another study showed possible relationship between lip cancer (SCC) and hydrochlorothiazide effect: 633 cases of lip cancer corresponded to 63,067 cases in the control group (population risk strategy was used). cumulative dose-effect relationship was shown using adjusted odds ratio which was equal to 2.1 (95 % CI: 1.7–2.6). The index was rising up to 3.9 (3.0–4.9) with administration of high-dose hydrochlorothiazide (~25000 mg) and up to 7.7 (5.7–10.5) with the maximal cumulative dose (~100000 mg) (see Special warnings and precautions for use).

#### *Pharmacokinetic properties.*

##### Linearity

Amlodipine, valsartan and hydrochlorothiazide show linear pharmacokinetics.

##### Amlodipine/valsartan/hydrochlorothiazide

Following oral administration of amlodipine/valsartan/hydrochlorothiazide in healthy volunteers, peak plasma concentrations of amlodipine, valsartan and hydrochlorothiazide were reached after 6 to 8 hours, 3 hours, and 2 hours, respectively. The rate and extent of absorption of amlodipine, valsartan and hydrochlorothiazide with the drug administration were the same as in case of administration of its individual ingredients as individual dosage forms.

##### Amlodipine

*Absorption.* After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations ( $C_{\max}$ ) of amlodipine were reached after 6 to 12 hours. Absolute bioavailability varied from 64% to 80%. Amlodipine bioavailability is unaffected by food ingestion.

*Distribution.* The volume of distribution is approximately 21 L/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of the circulating drug is bound to plasma proteins.

*Biotransformation.* Amlodipine is extensively (approximately 90%) metabolized in the liver to inactive metabolites.

*Elimination.* Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7 to 8 days. 10 % of amlodipine and 60% of amlodipine metabolites are excreted via urine.

#### Valsartan

*Absorption.* Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached after 2 to 4 hours. Mean absolute bioavailability is 23%. Food intake decreases valsartan exposure (as measured by the area under concentration-time curve – AUC) approximately by 40% and  $C_{max}$  approximately by 50%, although after 8 hours after administration, plasma valsartan concentrations are similar for the fasted and fed groups. However, this reduction in AUC is not accompanied by a clinically significant reduction in the therapeutic effect, and, therefore, valsartan can be given without regard to the timing of food.

*Distribution.* The volume of valsartan distribution at steady-state after intravenous administration is about 17 litres, indicating that valsartan is not distributed in tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly to serum albumin.

*Biotransformation.* Valsartan is not transformed significantly, since only about 20% of the dose is excreted as metabolites. A hydroxymetabolite has been identified in plasma at low concentrations (less than 10% of the AUC of valsartan). This metabolite is pharmacologically inactive.

*Elimination.* Valsartan is primarily eliminated in faeces (approximately 83% of the dose) and urine (around 13% of the dose), mainly as an unchanged medication. Following intravenous administration, plasma clearance of valsartan is around 2 L/hour and its renal clearance is 0.62 L/hour (about 30% of total clearance). The half-life of valsartan is 6 hours.

#### Hydrochlorothiazide

*Absorption.* The absorption of hydrochlorothiazide, after an oral dose is rapid ( $T_{max}$  approximately 2 hours). The increase in mean AUC is linear and dose-proportional if administered in the therapeutic range. There has been no change in the kinetics of hydrochlorothiazide with repeated dosing and accumulation has been minimal when administered once daily. Co-administration with food showed both an increase and decrease in the systemic availability of hydrochlorothiazide compared to administration upon fasting conditions. The severity of these effects is minor and has little clinical relevance. The absolute bioavailability of hydrochlorothiazide is 60–80% after oral administration.

*Distribution.* The apparent volume of distribution is 4 to 8 L/kg. Circulating hydrochlorothiazide is bound to serum proteins (40–70%), mainly to serum albumin. Hydrochlorothiazide also accumulates in erythrocytes in amounts that are 1.8-fold higher than plasma levels.

*Biotransformation.* Hydrochlorothiazide is eliminated as a parent drug.

*Elimination.* More than 95% of the absorbed dose is excreted unchanged via urine. The renal clearance consists of passive filtration and active secretion into the renal tubules. The half-life is 6 to 15 hours.

#### Special populations

##### *Children (aged under 18 years of age)*

No pharmacokinetic data are available in the pediatric population.

##### *Elderly (aged $\geq 65$ years)*

Time to  $C_{max}$  of amlodipine is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline causing an increase in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70% in the elderly than in the young patients, therefore, caution is required when increasing the dosage.

Systemic valsartan exposure is slightly elevated in the elderly compared to young patients but this has no clinical significance.

Some data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Since all three ingredients are equally well tolerated in younger and elderly patients, normal dose regimens are recommended.

##### *Renal impairment*

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. For the drug which renal clearance accounts for only 30% of total plasma clearance, no correlation was seen

between renal function and systemic valsartan exposure. Therefore, patients with mild to moderate renal impairment may receive the drug at the usual initial dose.

#### *Liver impairment*

Patients with liver function impairment have decreased clearance of amlodipine that results in an increase of AUC by approximately 40–60%. On average, in patients with mild to moderate chronic liver disease, valsartan AUC is 2-fold higher than in adult volunteers.

Caution should be exercised when administering the drug to patients with liver disease.

The amlodipine/valsartan/hydrochlorothiazide combination was not tested for genotoxicity or carcinogenicity as there was no evidence of any interaction between these substances. However, amlodipine, valsartan and hydrochlorothiazide have been tested individually for genotoxicity and carcinogenicity with negative results.

### **Clinical particulars.**

#### ***Therapeutic indications.***

Treatment of essential hypertension in adult patients whose blood pressure is adequately controlled by the combination of amlodipine, valsartan and hydrochlorothiazide taken either as three single-component formulations or two formulations one of which is a fixed combination.

#### ***Contraindications.***

- Hypersensitivity to the active substances, other sulphonamides, dihydropyridine derivatives, or to any of the excipients of the drug.
- Contraindicated to pregnant women and women who are planning to become pregnant (see Pregnancy or lactation)
- Hepatic impairment, biliary cirrhosis or cholestasis.
- Severe renal impairment (GFR <30 mL/min/1.73 m<sup>2</sup>), anuria and patients undergoing dialysis.
- Concomitant use of angiotensin receptor blockers (ARBs), including valsartan, or angiotensin converting enzyme inhibitors (ACEi) with aliskiren in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73 m<sup>2</sup>).
- Refractory hypokalemia, hyponatremia, hypercalcemia, and symptomatic hyperuricemia.
- Severe hypotension.
- Shock (including cardiogenic shock).
- Left ventricular outflow tract obstruction (e.g., hypertrophic obstructive cardiomyopathy and high grade aortic stenosis).
- Hemodynamically unstable heart failure following acute myocardial infarction.

#### ***Interaction with other medicinal products and other forms of interaction.***

No interaction studies with other medicinal products have been conducted with Tiara Trio<sup>®</sup>. The table below provides only information on the interaction of each individual active substance with other medicinal products.

However, it is important to take into account that Tiara Trio<sup>®</sup> may increase the hypotensive effect of other antihypertensive agents.

#### Concomitant use is not recommended

#### *Interactions related to both valsartan and hydrochlorothiazide*

##### *Lithium*

It was reported reversible elevation of serum lithium concentrations and toxicity with concomitant administration of lithium with ACEi, angiotensin II receptor blockers, including valsartan or thiazides, such as hydrochlorothiazide.

Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably increase further with the drug administration. Therefore, careful monitoring of serum lithium concentrations is recommended during concomitant use.

#### *Interactions related to valsartan*

*Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels*

If the administration of a medicinal product that affects potassium levels in combination with valsartan is considered, frequent monitoring of potassium plasma levels is advised.

*Interactions related to amlodipine*

*Grapefruit or grapefruit juice*

Administration of amlodipine with grapefruit or grapefruit juice is not recommended, since this combination enhances the effect of lowering blood pressure in some patients.

*Caution is required with concomitant use*

*Interactions related to amlodipine*

*CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir)*

Studies in elderly patients have shown that diltiazem inhibits amlodipine metabolism, possibly due to CYP3A4 (plasma concentrations increase by approximately 50% and the effect of amlodipine is enhanced). It cannot be ruled out that more potent CYP3A4 inhibitors (such as ketoconazole, itraconazole, ritonavir) may increase plasma concentrations of amlodipine more markedly than diltiazem.

Concomitant use of amlodipine and strong to moderate-acting CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides such as erythromycin and clarithromycin, verapamil or diltiazem) may lead to a marked elevation in amlodipine exposure. Clinical manifestation of this pharmacokinetic changes may appear more intense in elderly patients. Thus, clinical monitoring and dose adjustment may be necessary.

*CYP3A4 inducers (anticonvulsant agents [e.g., carbamazepine, phenobarbitone, phenytoin, fosphenytoin, primidone], rifampicin, St. John's wort)*

There is no data on the effect of CYP3A4 inducers on amlodipine. Co-administration of CYP3A4 inducers (e.g., rifampicin, St. John's wort) may lead to the decrease in amlodipine plasma concentrations. Therefore, blood pressure should be monitored and the dose adjusted during treatment with an inducer and after its discontinuation, if necessary.

Caution should be exercised when amlodipine is used with CYP3A4 inducers.

*Simvastatin*

Multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in simvastatin exposure compared to only simvastatin administration. It is recommended to reduce the daily dose of simvastatin to 20 mg in patients on amlodipine.

*Dantrolene (infusion)*

In animals, lethal cases of ventricular fibrillation and cardiovascular collapse were observed in association with hyperkalemia after administration of verapamil and dantrolene intravenously. Due to the risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine is avoided in patients susceptible to malignant hyperthermia and during the management of malignant hyperthermia.

*Interactions related to both valsartan and hydrochlorthiazide*

*Non-steroidal antiinflammatory drugs (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day), and non-selective NSAIDs*

NSAIDs can attenuate the antihypertensive effect of both angiotensin II blockers and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of Tiara Trio<sup>®</sup> and NSAIDs may lead to renal function impairment and an increase in serum potassium levels. Therefore, monitoring of kidney function at the beginning of treatment is recommended, as well as provide adequate hydration to the patient.

*Interactions related to valsartan*

*Uptake transporter inhibitors (rifampicin, cyclosporine) or efflux transporter inhibitors (ritonavir)*

The results of *in vitro* study with human liver tissue have shown that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of the uptake transporter inhibitors (rifampicin, cyclosporine) or efflux transporter inhibitors (ritonavir) may increase systemic valsartan exposure

*Interactions related to hydrochlorthiazide*

*Alcohol, anesthetics and sedatives*

Concomitant administration of thiazides and substances which have a hypotensive effect (for example, those which decrease sympathetic activity of the central nervous system or direct vasodilation) may potentiate orthostatic hypotension.

#### *Amlodipine*

Thiazides, including hydrochlorothiazide, may increase the risk of side effects caused by amlodipine.

#### *Anticholinergic agents and other medications which affect gastric motility*

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g., atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the gastric emptying rate.

And on the contrary, it is suggested that prokinetic substances, such as cisapride may decrease bioavailability of thiazides.

#### *Antidiabetic agents (e.g., insulin and oral antidiabetic agents)*

Thiazides may decrease glucose tolerance. Another dose adjustment of insulin and oral antidiabetic agents may be required.

#### *Metformin*

Metformin should be used with caution due to the risk of lactic acidosis induced by functional renal failure related to hydrochlorothiazide.

#### *Beta-blockers and diazoxide*

Concomitant use of thiazide diuretics, including hydrochlorothiazide, and beta-blockers may increase the risk of hyperglycemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycemic effect of diazoxide

#### *Carbamazepine*

Patients concomitantly receiving hydrochlorothiazide and carbamazepine may develop hyponatremia. Therefore, such patients should be warned of the possibility of hyponatremic reactions, and their condition should be monitored.

#### *Cyclosporine*

Concomitant treatment with cyclosporine may increase the risk of hyperuricemia and gout-type complications.

#### *Cytotoxic agents (e.g., cyclophosphamide, methotrexate)*

Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g., cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

#### *Digitalis glycosides*

Thiazide-induced hypokalemia or hypomagnesemia may occur as adverse effects favouring the onset of digitalis-induced cardiac arrhythmias.

#### *Iodine-based contrasting agent*

In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be rehydrated before administration.

#### *Ion-exchange resins*

Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. It may lead to subtherapeutic effects of thiazides. However, hydrochlorothiazide and resin intake should be displaced in time so as hydrochlorothiazide administration follows not sooner than 4 hours before or 4 to 6 hours after the resin intake which potentially reduces their interaction.

#### *Medications that affect potassium levels (kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives) and antiarrhythmic medications*

The hypokalemic effect of hydrochlorothiazide may increase with concomitant administration of kaliuretic diuretics, corticosteroids, laxatives, adrenocorticotrophic hormone (ACTH), amphotericin, carbenoxolone, penicillin G and salicylic acid derivatives and antiarrhythmic medications. If these medicinal products are prescribed with the amlodipine/valsartan /hydrochlorothiazide combination, monitoring of potassium plasma levels is advised.

#### *Medications that affect sodium levels*

Concomitant administration of diuretics and antidepressants, antipsychotics and antiepileptic drugs may potentiate their hyponatremic effect. Caution should be exercised with long-term use of these medicinal products.

#### *Medications which may cause torsades de pointes*

Taking into account hypokalemia risk, hydrochlorthiazide should be used with caution with medications that may cause *torsades de pointes*, in particular, with class Ia and III of antiarrhythmic medications as well as with some antipsychotic medications.

*Medicinal products used for treatment of gout (probenecid, sulfinpyrazone and allopurinol)*

Dose adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the levels of serum uric acid. Increase of dose of probenecid or sulfinpyrazone may be required.

Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

*Methyldopa*

There have been isolated reports of hemolytic anemia occurring with concomitant use of hydrochlorothiazide and methyldopa

*Non-depolarising skeletal muscle relaxants (e.g., tubocurarine)*

Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.

*Other antihypertensive drugs*

Thiazides enhance the antihypertensive effect of other antihypertensive drugs (guanethidine, methyldopa,  $\beta$ -blockers, vasodilators, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers and direct renin inhibitors).

*Pressor amines (e.g., norepinephrine, epinephrine)*

Hydrochlorothiazide may alleviate response to pressor amines such as norepinephrine. Clinical significance of this effect is undetermined and insufficient to stop their use.

*Vitamin D and calcium salts*

Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium. Concomitant use of thiazide diuretics may result in hypercalcemia (e.g., hyperparathyroidism, malignant tumours or vitamin D-related disorders) in susceptible patients as a result of increased calcium tubular reabsorption.

*Dual blockade of renin-angiotensin-aldosterone system (RAAS) with ARBs, ACEi or aliskiren*

Clinical data has shown that dual blockade of RAAS using co-administration of ACE inhibitors, ARB or aliskiren is associated with increased risk of side effects such as hypotension, hyperkalemia and kidney function impairment (including acute renal failure) compared to monotherapy with a substance that affects RAAS.

### ***Special warnings and precautions for use.***

The safety and efficacy of amlodipine in the treatment of hypertensive crisis have not been studied.

#### **Sodium-depleted and dehydrated patients**

Excessive hypotension, including orthostatic hypotension, was observed in 1.7% of patients who received maximal dose of Tiara Trio<sup>®</sup> (10 mg/320 mg/25 mg) compared to 1.8% of patients who received valsartan/hydrochlorthiazide (320 mg/25mg), 0.4% of patients who received amlodipine/valsartan (10 mg/320 mg) and 0.2% of patients who received hydrochlorthiazide /amlodipine (25 mg/10 mg) during a controlled study with patients who suffered for moderate or severe uncomplicated hypertension.

In patients with activated renin-angiotensin system (sodium-depleted and/or volume-depleted patients who receive high doses of diuretics) who use angiotensin II receptor blockers (ARBs), symptomatic hypotension may occur after the start of the drug intake. It is recommended that this condition is corrected prior to the initiation of Tiara Trio<sup>®</sup> or the patient should be closely monitored at the start of treatment.

If pronounced hypotension occurs with administration of Tiara Trio<sup>®</sup>, a patient should be placed in the supine position with raised legs and, if required, intravenous infusion of normal saline should be administered. Treatment may be continued once blood pressure is stabilized.

#### **Serum electrolyte changes**

##### ***Amlodipine/valsartan/hydrochlorothiazide***

According to the conducted studies, the opposite effect of 320 mg valsartan and 25 mg hydrochlorothiazide on serum potassium level approximately outweighs each other in many patients. In other patients one or another effect may be dominant.

Serum electrolyte levels should be monitored periodically for possible electrolyte imbalance.

Regular determination of serum electrolytes and potassium should be performed at appropriate intervals to prevent possible electrolyte imbalance, especially in patients with other risk factors such as impaired renal function, administration of other medicinal products or history of prior electrolyte imbalance.

#### *Valsartan*

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (e.g., heparin) is not recommended. Potassium levels should be monitored as appropriate.

#### *Hydrochlorothiazide*

It has been reported of hypokalemia during treatment with thiazide diuretics, including hydrochlorothiazide.

The drug administration should be initiated only after hypokalemia correction and any other co-existent hypomagnesemia. Thiazide diuretics may lead to hypokalemia manifestation or exacerbation of existing hypokalemia. Thiazide diuretics should be used with caution in patients with disorders that include potassium loss, for example salt-wasting type of nephropathy and prerenal (cardiogenic) kidney function impairment. If hypokalemia occurs during the therapy with hydrochlorothiazide, the medication administration should be discontinued unless stable correction of potassium balance is achieved.

Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with the development of hyponatremia and hypochloremic alkalosis or with the exacerbation of existing hyponatremia. Hyponatremia that is associated with neurological symptoms is observed (nausea, progressing disorientation, apathy). Treatment with hydrochlorothiazide should be initiated only after correction of existing hyponatremia. In case of severe or rapid hyponatremia during the use of the drug, its administration should be discontinued till the time when natremia is normalised.

Thiazides, including hydrochlorothiazide, enhance urinary magnesium excretion which may lead to hypomagnesemia. The use of thiazide diuretics reduces calcium excretion which can lead to hypercalcemia.

All patients receiving thiazide diuretics should be regularly monitored for electrolyte levels, particularly potassium, sodium and magnesium.

#### Renal impairment

Thiazide diuretics may speed up azotemia in patients with chronic kidney disease.

No dose adjustment of Tiara Trio® is required for patients with mild to moderate renal impairment ( $\text{GFR} \geq 30 \text{ mL/min/1.73 m}^2$ ). When Tiara Trio® is used in patients with renal impairment, regular monitoring of potassium, creatinine and uric acid serum levels is recommended.

Concomitant use of angiotensin receptor blockers, including valsartan, or ACE inhibitors with aliskiren is contraindicated in patients with renal impairment ( $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$ ).

The medicinal product is contraindicated to patients with severe renal failure, anuria or patients on dialysis.

#### Renal artery stenosis

Tiara Trio® should be used with caution for treatment of hypertension in patients with unilateral or bilateral renal artery stenosis or artery stenosis of a solitary kidney since blood urea and serum creatinine may increase in such patients.

#### Kidney transplantation

There is no experience of the safe use of Tiara Trio® in patients who have undergone a recent kidney transplantation.

#### Liver impairment

Valsartan is mostly eliminated as a parent drug in the bile. The half-life of amlodipine becomes prolonged and AUC values (area under the plasma concentration-time curve) becomes higher in patients with impaired liver function; dose recommendations have not been established. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg of valsartan. Therefore, Tiara Trio® is not indicated to this group of patients.

#### Angioedema

Quincke's edema, including swelling of the larynx and glottis that cause airway obstruction and/or facial edema and swelling of the lips, pharynx, and/or tongue, has been reported in patients treated

with valsartan. Some of these patients previously experienced Quincke's edema with other medicinal products including angiotensin-converting enzyme inhibitors (ACEi). The drug should be discontinued immediately in patients who develop Quincke's edema; re-administration is not recommended.

#### Heart failure and coronary artery disease/post-myocardial infarction

As a result of the renin-angiotensin-aldosterone system inhibition, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of RAAS, treatment with angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported regarding valsartan. Assessment of patients with heart failure or after myocardial infarction should always include renal function assessment.

In a long-term placebo-controlled study with amlodipine (PRAISE-2) in patients with heart failure of non-ischemic origin class III and IV according to NYHA classification (New York Heart Association), the rate of lung edema cases with amlodipine use was higher despite insignificant difference in manifestation or worsening of heart failure compared to such with the use of placebo.

Patients with congestive cardiac failure should use calcium channel blockers, including amlodipine, with caution for they may increase the risk of cardiovascular events and lethal outcome.

Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of 10 mg/25 mg/320 mg, since available data in these patient populations are limited.

#### Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with all other vasodilators, special caution is indicated in patients with mitral stenosis and significant aortic stenosis or obstructive hypertrophic cardiomyopathy.

#### Pregnancy

Treatment with ARB II should not be initiated during pregnancy. If it is necessary to continue the therapy with ARB II, patients who are planning to become pregnant have to be transferred to treatment with other options of antihypertensive medications which have an established safety profile for use in pregnant women. If the pregnancy occurred, treatment with ARB II should be discontinued immediately and, if deemed necessary, alternative therapy should be started.

#### Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with the angiotensin II receptor blocker valsartan, since their renin-angiotensin system is not activated. Therefore, Tiara Trio<sup>®</sup> is not recommended in this patient population.

#### Systemic lupus erythematosus

It has been reported that thiazide diuretics, including hydrochlorothiazide, exacerbate the course of systemic lupus erythematosus.

#### Other disorders of metabolism

Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required.

Since Tiara Trio<sup>®</sup> contains hydrochlorothiazide, it is contraindicated in symptomatic hyperuricemia. Hydrochlorothiazide may elevate serum uric acid levels due to decreased clearance of uric acid and may cause or exacerbate hyperuricemia as well as acute gout attack in susceptible patients.

Thiazides may reduce urinary calcium excretion and intermittent and slight elevations of serum calcium in the absence of known disorders of calcium metabolism. The medication administration should be discontinued if hypercalcemia occurs during the treatment. During the therapy with thiazides serum calcium level should be assessed at some time intervals. Marked hypercalcemia may be the evidence of latent hyperparathyroidism. Thiazides should be discontinued prior to parathyroid function tests.

#### Photosensitivity

Reports on cases of photosensitivity reactions were obtained as a result of administration of thiazide diuretics. If photosensitivity reactions occur during treatment with Tiara Trio<sup>®</sup>, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas from the sun or artificial UV radiation.

#### Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Hydrochlorothiazide, sulphonamide or sulphonamide derivatives may induce idiosyncratic reaction that results in choroidal effusion with visual field defect, acute transient myopia and angle-closure glaucoma. Symptoms included the acute onset of decreased visual acuity or ocular pain that typically occurred within hours to one week of treatment initiation. Untreated angle-closure glaucoma may lead to permanent vision loss.

First of all, it is necessary to discontinue hydrochlorothiazide as soon as possible. Prompt medical or surgical treatment should be considered if the intraocular pressure remains uncontrolled. Risk factors of angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

#### General warnings

Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor blockers. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

#### Elderly (aged $\geq 65$ years)

Caution is recommended in elderly patients, particularly at the maximum dose of Tiara Trio<sup>®</sup>, 10 mg/320 mg/25 mg, since available data in this patient population are limited. Blood pressure should be monitored in these patients.

#### *Dual blockade of RAAS*

There is evidence that concomitant use of ACE inhibitors, ARB II or aliskiren increases the risk of hypotension, may lead to increased incidence of hypotension, hyperkalemia and renal function impairment (including acute renal failure). Therefore, dual blockade of RAAS due to concomitant use of ACE inhibitors, ARB II or aliskiren is not recommended.

If dual blockade is needed, it should be performed under the thorough follow-up of the specialist and constant kidney function monitoring, electrolytes level and blood pressure. Concomitant use of ACE inhibitors and ARB II is not recommended in patients with diabetic nephropathy.

#### *NMSC*

In two epidemiological studies at the Danish Cancer Registry a possible increase of NMSC (BCC and SCC) was noted that has been associated with an increase of cumulative dose of hydrochlorothiazide. Photosensitisation effect of hydrochlorothiazide may be a cause of NMSC.

Patients who receive hydrochlorothiazide should be informed about the risk of NMSC and necessity of the regular skin check-up regarding the presence of new lesions and immediate notification about any suspicious skin lesions.

Possible preventive measures, such as restriction of the sun radiation exposure and UV light; in case of exposure, patients should be advised to wear special protection to minimise the risk of skin cancer. Suspicious skin lesions should be investigated immediately, including histological examination of biopsy specimens potentially. Hydrochlorothiazide administration should be reviewed in patients who had a history of NMSC (see Side effects).

#### *Important information on excipients.*

This medication contains sodium entities, therefore, patients who follow sodium-controlled diet should administer this medication with caution.

#### *Pregnancy or lactation.*

##### Pregnancy

##### *Amlodipine*

The safety of amlodipine during pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses. Use in pregnancy is recommended only in cases when there is no safer option of the medicinal product and when the disease itself carries greater risk for the mother and embryo.

##### *Valsartan*

The drug is contraindicated in pregnant women and women who are planning to become pregnant. If pregnancy is confirmed during the use of this medicinal product, the latter should be stopped immediately and, if necessary, replaced by another medicinal product approved for use by pregnant women.

##### *Hydrochlorothiazide*

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Data from animal studies is not sufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise fetoplacental perfusion and cause fetal and neonatal effects, such as jaundice, electrolyte disturbance and thrombocytopenia and may be associated with other side effects observed in adults.

#### Amlodipine/valsartan/hydrochlorothiazide

There is no experience in administration of Tiara Trio<sup>®</sup> to pregnant women. Based on the existing data regarding the ingredients, it is possible to state that the use of Tiara Trio<sup>®</sup> is contraindicated during pregnancy.

#### Lactation

Amlodipine is excreted in the breast milk. Percent of the maternal dose which is received by an infant was assessed by an interquartile range of 3 – 7, maximum 15%. Effect of amlodipine on an infant is unknown. There is no data on the use of valsartan during breast feeding. Hydrochlorothiazide is excreted in the breast milk in small amounts. Thiazides at high doses that lead to high urine output may interfere with breast milk production.

The use of Tiara Trio<sup>®</sup> is contraindicated during breast-feeding.

#### Fertility

There are no clinical studies related to Tiara Trio<sup>®</sup> administration and fertility.

#### Valsartan

Valsartan have not shown any harmful effect on reproductive system of male and female rats with oral administration of 200 mg/kg/day. This dose is 6-fold higher than the maximal recommended human dose calculated in milligram per meter square (calculations suggest oral dose 320 mg/day for a patient with body weight 60 kg).

#### Amlodipine

In some patients who did not receive calcium channel blockers reverse biochemical changes of spermatozoid head were registered. Clinical data regarding potential effect of amlodipine on fertility is not sufficient. In one study with rats negative effect on male fertility was discovered.

#### *Effects on ability to drive and use machines.*

Patients taking Tiara Trio<sup>®</sup> may experience dizziness or fatigue occasionally after the drug intake, therefore, they should take this into account during driving vehicles or using potentially dangerous machines.

Amlodipine can have mild or moderate effects on the ability to drive and use machines. If patients during treatment with amlodipine suffer from dizziness, headache, fatigue or nausea, their ability to react may be impaired.

#### ***Posology and method of administration.***

##### Method of administration

Tiara Trio<sup>®</sup> can be taken with or without food. Tablets should be swallowed whole with some water, at the same time of the day and preferably in the morning.

##### Posology

The recommended dose of Tiara Trio<sup>®</sup> is one tablet daily, preferably in the morning.

Before switching to Tiara Trio<sup>®</sup>, patients should be well-controlled with stable doses of the single entity medications taken simultaneously at the same time. The dose of Tiara Trio<sup>®</sup> should correspond to the doses of the individual ingredients of the combination at the time of switching.

The maximal recommended dose of Tiara Trio<sup>®</sup> is 10 mg/25 mg/320 mg.

##### Special populations

##### *Renal impairment*

Due to hydrochlorothiazide, Tiara Trio<sup>®</sup> is contraindicated for use in patients with anuria and severe renal impairment (creatinine clearance <30 mL/min).

Co-administration of Tiara Trio<sup>®</sup> with aliskiren is contraindicated in patients with renal impairment (GFR <30 mL/min/1.73 m<sup>2</sup>).

No adjustment of the initial dose is required for patients with mild to moderate renal impairment.

### *Diabetes mellitus*

Co-administration of Tiara Trio<sup>®</sup> and aliskiren is contraindicated for use in patients with diabetes mellitus.

### *Liver impairment*

Due to the presence of hydrochlorothiazide and valsartan in the composition, Tiara Trio<sup>®</sup> is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment without cholestasis, the maximal recommended dose is 80 mg of valsartan, therefore, Tiara Trio<sup>®</sup> is not suitable for use in this patient population.

Amlodipine dose recommendations have not been established in patients with mild to moderate hepatic impairment.

Once switching patients with hypertension and liver function impairment to Tiara Trio<sup>®</sup>, the lowest acceptable amlodipine dose should be used.

### *Heart failure and coronary artery disease*

There is limited experience of Tiara Trio<sup>®</sup> use, especially at the maximum dose in patients with heart failure and coronary artery disease. Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of Tiara Trio<sup>®</sup>, 10 mg/25 mg/320 mg.

### *Elderly (aged ≥65 years)*

Caution is recommended in elderly patients, particularly at the maximum dose of Tiara Trio<sup>®</sup>, 10 mg/25 mg/320 mg, since available data in this patient population is limited. Blood pressure should be monitored in these patients.

Once switching elderly patients to Tiara Trio<sup>®</sup>, the lowest acceptable amlodipine dose should be used.

### *Pediatric populations*

There is no relevant data on use of Tiara Trio<sup>®</sup> in the pediatric population (patients younger than 18 years of age) in case of essential hypertension.

### *Children.*

The safety and efficacy in the pediatric population have not been established, thus the drug is not administered to this age group.

## ***Overdose.***

### Symptoms

There is no experience of an overdose with Tiara Trio<sup>®</sup>. The major possible symptom of an overdose is pronounced hypotension associated with dizziness. An overdose with amlodipine may result in marked peripheral vasodilation and reflex tachycardia. Marked and potentially prolonged systemic hypotension, including shock with fatal outcome, has been reported.

### Treatment

### *Amlodipine/valsartan/hydrochlorothiazide*

Clinically significant hypotension due to the overdose with Tiara Trio<sup>®</sup> calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function and monitoring of circulating blood volume and urine output. The patient should be placed in the supine position with raised lower extremities. Vasoconstrictors may be helpful in restoring vascular tone and blood pressure provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

### *Amlodipine*

If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or within two hours has shown a significant decrease of amlodipine absorption.

Amlodipine is unlikely to be removed by hemodialysis.

### *Valsartan*

Valsartan is unlikely to be removed by hemodialysis.

### *Hydrochlorothiazide*

An overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalemia, hyponatremia) and hypovolemia as a result of excessive diuresis. The most common symptoms of

overdose are nausea and somnolence. Hypokalemia may result in muscle spasms and/or exacerbation of arrhythmia associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic agents.

The extent to which hydrochlorothiazide is cleared out by hemodialysis has not been established.

### ***Side effects.***

Safety profile of use of combination amlodipine/valsartan/hydrochlorothiazide which is presented below is based on clinical studies and known safety profile of its single entities: amlodipine, valsartan and hydrochlorothiazide.

All side effects are ranked according to System Organ Class (MedDRA) and incidence and are presented regarding the combination amlodipine/valsartan/hydrochlorothiazide and separately regarding every single entity: very common ( $\geq 1/10$ ), common ( $\geq 1/100 - < 1/10$ ), uncommon ( $\geq 1/1\,000 - < 1/100$ ), rare ( $\geq 1/10\,000 - < 1/1\,000$ ), very rare ( $< 1/10\,000$ ), unknown (cannot be assessed based on existing data).

#### **Side effect incidence regarding the combination amlodipine/valsartan/hydrochlorothiazide:**

*Eye disorders:* uncommon – visual disturbance.

*Ear and vestibular disorders:* uncommon – vertigo.

*Respiratory, thoracic and mediastinal disorders:* uncommon – cough, dyspnea, throat irritation.

*Gastrointestinal disorders:* common – dyspepsia; uncommon – abdominal discomfort, pain in the upper abdomen, breath odour, diarrhea, dry mouth, nausea, vomiting.

*Renal and urinary disorders:* common – pollakiuria; uncommon – elevated serum creatinine, acute kidney failure.

*Metabolism and nutrition disorders:* common – hypokalemia; uncommon – anorexia, hypercalcemia, hyperlipidemia, hyperuricemia, hyponatremia.

*Nervous system disorders:* common – dizziness, headache; uncommon – abnormal coordination, postural dizziness, exertional dizziness, dysgeusia, lethargy, paresthesia, peripheral neuropathy, drowsiness, syncope, tremor.

*Psychiatric disorders:* uncommon – insomnia/ sleep disturbances

*Cardiac disorders:* uncommon – tachycardia.

*Vascular disorders:* common – hypotension; uncommon – orthostatic hypotension, phlebitis, thrombophlebitis.

*Skin and subcutaneous tissue disorders:* uncommon – itching, hyperhidrosis.

*Musculoskeletal and connective tissue disorders:* uncommon – back pain, joint swelling, muscle weakness, myalgia, limb pain.

*Reproductive system and breast disorders:* uncommon – impotence.

*General disorders and local reactions:* common – fatigue, swelling; uncommon – abasia, gait disturbances, asthenia, discomfort, malaise, non-cardiac chest pain.

*Investigations:* uncommon – increased urea nitrogen, increased blood uric acid, decreased serum potassium, weight gain.

#### **Side effect incidence related to amlodipine**

*Eye disorders:* uncommon – visual impairment, visual disturbance.

*Ear and vestibular disorders:* uncommon – tinnitus.

*Respiratory, thoracic and mediastinal disorders:* uncommon – dyspnoea, rhinitis; very rare – cough.

*Gastrointestinal disorders:* common – nausea, vomiting, abdominal discomfort, pain in the upper abdomen; uncommon – changes in the bowel habit, diarrhea, dry mouth, dyspepsia; very rare – gastritis, gingival hyperplasia, pancreatitis.

*Hepatobiliary disorders:* very rare – hepatitis, intrahepatic cholestasis, jaundice, elevated liver enzymes, including elevated serum bilirubin (mostly related to cholestasis).

*Renal and urinary disorders:* uncommon – dysuria, micturition disorder, nocturia.

*Metabolism and nutrition disorders:* very rare – hyperglycemia.

*Nervous system disorders:* common – dizziness, headache, somnolence; uncommon – dysgeusia, paresthesia, syncope, tremor, hyposthesia; very rare – hypertension, peripheral neuropathy, neuropathy; unknown frequency – extrapyramidal syndrome.

*Psychiatric disorders:* uncommon – depression, insomnia/sleep disturbances, mood swings; rare –

confusion.

*Cardiac disorders:* common – palpitation; very rare – arrhythmia (including bradycardia, ventricular tachycardia, atrial fibrillation), myocardial infarction.

*Vascular disorders:* common – flushes; uncommon – hypotension; very rare – vasculitis.

*Blood and lymphatic system disorders:* very rare – leukopenia, thrombocytopenia, sometimes associated with purpura.

*Immune system disorders:* very rare – hypersensitivity.

*Skin and subcutaneous tissue disorders:* uncommon – itching, rashes, purpura, alopecia, exanthema, hyperhidrosis, skin discoloration; very rare – urticaria, angioedema, erythema multiforme, photosensitivity reactions (see Special warnings and precautions for use (Photosensitivity), exfoliative dermatitis, Stevens-Johnson syndrome, Quincke's edema; unknown frequency – necrotizing vasculitis and toxic epidermal necrolysis.

*Musculoskeletal and connective tissue disorders:* common – ankle swelling; uncommon – arthralgia, back pain, muscle cramps, myalgia.

*Reproductive system and breast disorders:* uncommon – gynecomastia, impotence.

*General disorders and local reactions:* common – fatigue, swelling; uncommon – pain, asthenia, discomfort, malaise, non-cardiac chest pain.

*Investigations:* uncommon – weight gain/weight loss.

Side effect incidence related to valsartan:

*Ear and vestibular disorders:* uncommon – vertigo.

*Respiratory, thoracic and mediastinal disorders:* uncommon – cough.

*Gastrointestinal disorders:* uncommon – abdominal discomfort, pain in the upper abdomen.

*Hepatobiliary disorders:* unknown frequency – elevated liver enzymes, including elevated serum bilirubin.

*Renal and urinary disorders:* unknown frequency – elevated serum creatinine, renal failure and kidney function impairment.

*Vascular disorders:* unknown frequency – vasculitis.

*Blood and lymphatic system disorders:* unknown frequency – decreased hemoglobin and hematocrit levels, neutropenia, thrombocytopenia, sometimes associated with purpura.

*Immune system disorders:* unknown frequency – hypersensitivity.

*Skin and subcutaneous tissue disorders:* unknown frequency – rashes, itching, bullous dermatitis, angioedema.

*Musculoskeletal and connective tissue disorders:* unknown frequency – myalgia.

*General disorders and local reactions:* uncommon – fatigue.

*Investigations:* unknown frequency – increased blood potassium level.

Side effect incidence related to hydrochlorthiazide:

*Eye disorders:* rare – visual disturbance; unknown frequency – acute angle-closure glaucoma, choroidal effusion.

*Respiratory, thoracic and mediastinal disorders:* very rare – respiratory distress, pulmonary edema, pneumonitis.

*Gastrointestinal disorders:* common – loss of appetite, nausea, vomiting; rare – constipation, diarrhea, abdominal discomfort, upper part abdominal pain; very rare – pancreatitis.

*Hepatobiliary disorders:* rare – intrahepatic cholestasis, jaundice.

*Renal and urinary disorders:* rare – renal failure and kidney function impairment; unknown frequency – renal dysfunction, acute renal failure.

*Metabolism and nutrition disorders:* very common – hypokalemia; common – hyperuricemia, hypomagnesemia, hyponatremia; rare – hypercalcemia, hyperglycemia, increased metabolic signs of diabetes; very rare – hyperchloremic alkalosis.

*Nervous system disorders:* rare – dizziness, headache, paresthesia.

*Psychiatric disorders:* rare – depression, insomnia/sleep disturbance.

*Cardiac disorders:* rare – arrhythmia (including bradycardia, ventricular tachycardia, atrial fibrillation), myocardial i

*Vascular disorders:* common – orthostatic hypotension.

*Blood and lymphatic system disorders:* rare – thrombocytopenia, sometimes associated with purpura; very rare – leukopenia, neutropenia, agranulocytosis, bone marrow suppression; unknown frequency

*Immune system disorders:* very rare – hypersensitivity.

*Skin and subcutaneous tissue disorders:* common – rashes, urticaria; rare – purpura, photosensitivity reactions (see Special warnings and precautions for use (Photosensitivity)); very rare – cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, necrotizing vasculitis and toxic epidermal necrolysis, exfoliative dermatitis; unknown frequency – erythema multiforme/

*Benign, malignant and unidentified lesions (including cysts and polyps):* unknown frequency – NMSC (basal cell carcinoma (BCC) and squamous cell carcinoma (SCC))

*Musculoskeletal and connective tissue disorders:* unknown frequency – muscle cramps.

*Reproductive system and breast disorders:* common – impotence.

*General disorders and local reactions:* unknown frequency – chills, asthenia.

*Investigations:* very common – increase in lipid profile; rare – glucosuria.

#### Description of chosen side effects

NMSC: Based on epidemiological study results a cumulative dose-dependent relationship between hydrochlorothiazide administration and NMSC is observed (see Special warnings and precautions for use).

#### Reported suspected adverse reactions.

Reporting suspected adverse reactions after registration of a medicinal product is an important procedure. This allows for continued monitoring of the benefit/risk ratio for the respective drug. Healthcare providers should be informed of any suspected adverse reactions through the national alert system.

***Shelf life.*** 2 years.

#### **Special precautions for storage.**

Keep in the original package at  $\leq 25^{\circ}\text{C}$ . Keep out of reach of children.

#### **Packaging**

14 tablets in a blister; 1 or 2 blisters in a box.

**Category of release.** Prescription medicine.

**Manufacturer.** PrJSC Pharmaceutical Firm “Darnitsa”.

#### **The manufacturer's location and address of the place of business.**

13 Boryspilska Street, Kyiv, 02093 Ukraine

#### **Date of last revision.**