Zetakardoval

Film Coated Tablets

5/160, 5/320, 10/160, 10/320

Not to be used during pregnancy it can cause injury or death of developing foetus

Description

Zetakardoval 5/160, Zetakardoval 10/160, Zetakardoval 5/320 and Zetakardoval 10/320 are available as film-coated tablets in four strengths containing amlodipine besylate (5 or 10 mg) and valsartan (160 mg or 320mg) as: 5/160 mg, 10/160 mg, 5/320 mg and 10/320 mg.
Excipients: Cellactose 80, Polyplasdone xl-10, PVP K30, Aerosil 200, Magnesium stearate, and Opadry pink (5/160) or Opadry yellow (5/320) or Opadry green (10/160) or Opadry grey (10/320).

Pharmacology

Pharmacodynamics

Pharmacotherapeutic group: dihydropyridine derivatives (amlodipine) combinations with angiotensin II antagonists, plain (valsartan).

ZETAKARDOVAL combines two antihypertensive compounds with complementary mechanisms to contr blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II (Ang II) antagonist class of medicines. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine: The amlodipine component inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in bloo pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridin binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Plasma concentrations correlate with effect in both young and elderly patients. In hypertensive patients wi normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance a an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fracti or proteinuria. As with other calcium channel blockers, haemodynamic measurements of cardiac function rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or o left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact anim and humans, even when co-administered with beta blockers to humans. Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertensio or angina, no adverse effects on electrocardiographic parameters were observed.

Valsartan: Valsartan is an orally active, potent and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The AT2 receptor subtype has not been definitely shown to be associated with cardiovascular homeostasis. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has about a 20,000-fold greater affinity for the AT1 receptor than for the AT2 receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with cough.

Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate. In most patients after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours and the peak reduction in blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dose administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy.
Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

Pharmacokinetics

Amlodipine: After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.
Volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins in hypertensive patients.

Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites. 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 7–8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Valsartan: Peak plasma concentrations are reached 2 to 4 hours after dosing. The amount absorbed varies widely. Mean absolute bioavailability is 23% and the bioavailability relative to an oral solution is 59%.

The pharmacokinetics of valsartan are linear over the dose range 80 - 320 mg. There is no change in the kinetics of valsartan on repeated administration and little accumulation when dosed once daily. Plasma concentrations are similar in males and females.

When valsartan is given with food, the area under the plasma concentration-time curve (AUC) of valsartan is reduced by 48% although, from about 8 h post dosing, plasma valsartan concentrations are similar for the fed and fasted group.

Valsartan is highly bound to serum protein (94-97%), mainly serum albumin. Steady-state volume of distribution is low (about 17 L) indicating that valsartan does not distribute into tissues extensively.

- Severe renal impairment (GFR<30 ml/min/1.73 m2) and patients undergoing dialysis;
- Pregnancy;
- Concomitant use with aliskiren-containing products in patients with Type 2 diabetes mellitus (see "INTERACTIONS WITH OTHER MEDICINES") or renal impairment (GFR < 60ml/min/1.73m2).

Precautions:

Hypotension, Sodium and/or Volume Depleted Patients
Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with (Amlodipine/valsartan combination). In patients with an activated renin-angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of Zetakardoval or close medical supervision at the start of treatment is recommended.

If hypotension occurs with Zetakardoval, the patient should be placed in the supine position and, if necessary, given an i.v. infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Increased Angina and/or Acute Myocardial Infarction
Rarely patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina and/or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase.

Beta-blocker Withdrawal
Amlodipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Renal Artery Stenosis
Zetakardoval should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis, stenosis to a solitary kidney. Short-term administration of valsartan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, since other drugs that affect the renin-angiotensin-aldosterone system (RAAS) may increase blood urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis, monitoring of both parameters is recommended as a safety measure.

Kidney Transplantation
To date there is no experience of the safe use of Zetakardoval in patients who have had a recent kidney transplantation.

Aortic and Mitral Valve Stenosis, Hypertrophic Obstructive Cardiomyopathy
As with all other vasodilators, special caution is indicated when using Zetakardoval in patients with haemodynamically relevant aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Hyperkalaemia
Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) should be used with caution and with frequent monitoring of potassium.

Concomitant Use with ACE Inhibitors

Valsartan does not undergo extensive biotransformation. Only approximately 25% of absorbed drug is metabolised. The primary metabolite is valeryl 4-hydroxy valsartan, which is pharmacologically inactive. The enzyme(s) responsible for valsartan metabolism have not been identified.
Valsartan shows bi-exponential decay kinetics with a t1/2α of about 1h and a t1/2 β of about 9.5 hours. After oral dosing, 83% of the dose is excreted in the faeces and 13% in the urine, mainly as unchanged compound. Following intravenous administration, renal clearance of valsartan accounts for about 30% of total plasma clearance. Plasma clearance is relatively slow (about 2 L/h) when compared with hepatic blood flow (about 90 L/h).

Amlodipine/valsartan: Following oral administration of (Amlodipine/valsartan combination) peak plasma concentrations of amlodipine and valsartan are reached in 6-8 and 3 hours, respectively. The rate and extent of absorption of (Amlodipine/valsartan combination) are equivalent to the bioavailability of amlodipine and valsartan when administered as individual tablets.

Pharmacokinetics in children: No pharmacokinetic data are available in the paediatric population.

Pharmacokinetics in the elderly (aged 65 years or older): Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in AUC and elimination half-life.
Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly compared to younger patients.

Pharmacokinetics in patients with impaired renal function: The pharmacokinetics of amlodipine is not significantly influenced by renal impairment.
As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, there is no apparent correlation between renal function (measured by creatinine clearance) and systemic exposure to valsartan (measured by AUC) in patients with different degrees of renal failure. A trial in 5 normotensive patients undergoing haemodialysis demonstrated that complete loss of renal function does not lead to a gross increase in the exposure to valsartan and does not have a major impact on the kinetics of valsartan. This study also confirmed that valsartan is not removed from the plasma by haemodialysis.

Pharmacokinetics in patients with impaired hepatic function: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60% in AUC. In a small number of patients with mild to moderate hepatic impairment given single doses of 5 mg, amlodipine half-life has been prolonged. Worsening of liver function test values may occur.
About 70% of the absorbed valsartan dose is excreted in the bile, mainly as unchanged compound. The AUC with valsartan has been observed to approximately double in patients with mild or moderate hepatic impairment including patients with biliary obstructive disorders (see **Precautions - Impaired hepatic function**). There are no data available on the use of valsartan in patients with severe hepatic dysfunction (see **Contraindications**).
Care should be exercised in patients with liver disease (see **Precautions**).

Indications:
Zetakardoval is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed dose combination.

Contraindications:
- Hypersensitivity to the active substances, dihydropyridine derivatives, or to any of the excipients;
- Severe hepatic impairment; biliary cirrhosis and cholestasis;

Use in Patients with Hepatic Impairment
Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolized by the liver. In patients with mild to moderate hepatic impairment without cholestasis, Zetakardoval should be used with caution (see **Pharmacokinetics - Impaired hepatic function**) and careful monitoring of liver function tests should be performed. The daily dose of (Amlodipine/valsartan combination) should not exceed 5/80 mg. Patients with severe hepatic impairment, biliary cirrhosis or cholestasis should not take Zetakardoval (see **Contraindications**).

Use in Patients with Renal Impairment
No dosage adjustment of Zetakardoval is required for patients with mild to moderate renal impairment. Monitoring of creatinine and potassium levels is advised for patients with moderate renal impairment. Patients with severe renal impairment should not take Zetakardoval (see **Contraindications**).

Primary Hyperaldosteronism
Patients with primary hyperaldosteronism will not generally respond to antihypertensive drugs acting through the renin-angiotensin aldosterone system therefore use of Zetakardoval in these patients is not recommended.

Children and Adolescents
The safety and efficacy of Zetakardoval in children and adolescents (below the age of 18 years) have not been established.

Effects on Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles or using machines it should be taken into account that occasionally dizziness or weariness may occur.

Carcinogenicity
No carcinogenicity studies have been conducted with the amlodipine/valsartan combination.

Valsartan: In animal studies, there was no clear evidence of carcinogenic activity when valsartan was administered in the diet to male and female mice at doses up to 160 mg/kg/day for two years, but systemic exposure (plasma AUC value) at this dose level was lower than that achieved in humans. There was no clear evidence of carcinogenic activity in male or female rats at up to 200 mg/kg/day with plasma concentrations approximately 1.5 times the concentrations achieved in humans (based on AUC) at the maximum recommended dose (320 mg).

Amlodipine: The carcinogenic potential of amlodipine has not been fully elucidated. Amlodipine did not induce any tumours when tested in rats at oral doses up to 2.5 mg/kg. This dose gave rise to plasma levels that are similar to those achieved clinically.

Genotoxicity
No genotoxicity studies have been conducted with the amlodipine/valsartan combination.
Valsartan: Genotoxicity studies showed that valsartan does not cause gene mutation in bacterial or mammalian cells, nor does it induce chromosomal damage *in vitro* or *in vivo*.
Amlodipine did not induce gene mutation in bacteria or mouse lymphoma cells, and was not clastogenic in human lymphocytes, Chinese hamster V79 fibroblast cells (*in vitro*), or mouse bone marrow cells (*in vivo*).

Effects on Fertility

Concomitant use of an angiotensin II receptor blocker and an ACE inhibitor may increase the risk of hyperkalaemia, renal failure, hypotension and syncope.

Angioedema
Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported in patients treated with valsartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Zetakardoval should be immediately discontinued in patients who develop angioedema, and Zetakardoval should not be re-administered.

Dual blockade of the Renin-Angiotensin System (RAS)
Caution is required while co-administering ARBs, including valsartan, with other agents blocking the RAS such as ACEIs or aliskiren (see "Interactions with Other Medicines").

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACEinhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Use in Patients with Heart Failure/Post-myocardial Infarction
In general, calcium channel blockers should be used with caution in patients with heart failure. As a consequence of inhibiting the renin-angiotensin-aldosterone system, 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 the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan.

Use of valsartan in patients with heart failure or post-myocardial infarction commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed. Patients with more complicated post-myocardial infarction courses may be at increased risk for hypotension and/or renal dysfunction. Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction. An assessment of renal function should always be conducted in patients with heart failure or post-myocardial infarction.

An increase in the mortality rate among patients who received a combination of valsartan, ACE inhibitors and beta blockers has been observed in clinical trials. Concurrent administration of ACE inhibitors, beta blockers and valsartan is not recommended.

Hepatic Injury
Cases of clinically significant liver disease have occurred with some angiotensin II receptor antagonists. Hepatitis has been reported rarely with valsartan.

No specific fertility studies were conducted with valsartan/amlodipine combination; however, testes, ovari and secondary sex organs were evaluated in other toxicity studies with this combination. The primary and secondary sex organs were not affected in these toxicity studies, in which rats and marmosets were treated with this combination for up to 13 weeks.

Valsartan: Fertility of male and female rats was not affected at oral doses up to 200 mg/kg/day, with systemic exposure similar to that in human patients at the maximum recommended dose.

Amlodipine: Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility but in one rat study, adverse effects were found on male fertility.

Use in Pregnancy (Category D)
Zetakardoval must not be used during pregnancy (see **Contraindications**) or in women planning to becom pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, Zetakardoval must be discontinued as soon as possible.

Drugs that act on the renin-angiotensin-aldosterone system (RAAS) can cause foetal and neonatal morbidi and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors (a specific class of drugs acting on the RAAS).

Due to the mechanism of action of angiotensin II antagonists, a risk to the foetus cannot be excluded. The use of drugs that act directly on the renin-angiotensin-aldosterone system (RAAS) during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunctio when pregnant women have inadvertently taken valsartan. Pregnant women who are taking angiotensin II receptor antagonists (ARAs) should be changed as quickly as possibly to other antihypertensive medicati to maintain normal blood pressure. It is generally advisable not to use ARAs for the management of hypertension in women who are likely to become pregnant.
Calcium channel blockers carry the potential to produce foetal hypoxia associated with maternal hypotension. Accordingly they should not be used in pregnant women unless the potential benefit outwei the risk to the foetus.

In the event that neonates are exposed to Zetakardoval *in utero* and oliguria or hypotension occurs, direct attention towards support of blood pressure and renal perfusion. Exchange transfusions or dialysis may b required as a means of reversing hypotension and/or substituting for disordered renal function.

There was no evidence of teratogenicity in rats dosed with the amlodipine/valsartan combinations during organogenesis at doses up to 20:320 mg/kg/day PO. Foetotoxicity was observed in association with mate toxicity (≥10:160 mg/kg/day) in rats at amlodipine/valsartan doses of 20:320 mg/kg/day and included decreased fetal weights, dilated ureters and delayed/incomplete ossification. The (AUC) exposures at the doses were 3-10x the expected human exposure to amlodipine/valsartan at the maximum proposed clinic dose (10:160mg/day).

No teratogenic effects were observed when valsartan alone was administered orally to mice and rats at a dose of 600 mg/kg/day and to rabbits at a dose of 10 mg/kg/day during the period of organogenesis.

However, foetal losses were observed at the highest dose level in rabbits, and foetal weight was reduced at 600 mg/kg/day in rats and at 5 mg/kg/day in rabbits.

Administration of 600 mg/kg/day valsartan to rats prior to parturition and during lactation caused a decrease in birth weight, a reduction in post-natal growth and survival, and a slight delay in physical development of the offspring. A reduction of red blood cell parameters and evidence of changes in renal haemodynamics were observed at 200-600 mg/kg/day.

No teratogenic effects were found when 18 mg/kg/day amlodipine (base) was administered in rats or 10 mg/kg/day in rabbits. Amlodipine (7mg/kg/day as base) administered orally to rats at or near parturition induced a prolongation of gestation time, an increase in number of stillbirths and decreased post-natal survival.

Use in Lactation
It is not known whether valsartan and/or amlodipine are excreted in human milk. There are no studies with the amlodipine besylate/valsartan combination in lactating animals. Valsartan was excreted in the milk of lactating rats. A peri/postnatal study in rats with valsartan showed reductions in postnatal growth and survival, and a slight delay in physical development of the offspring when valsartan was administered to rats prior to parturition and during lactation at 600 mg/kg/day. No effects were observed at 200 mg/kg/day. It is therefore not advisable for women who are breast-feeding to use Zetakardoval.

Interactions with other Medicines
No drug interaction studies have been conducted with Zetakardoval and other drugs, although studies have been conducted with the individual amlodipine and valsartan components, as described below.

Other antihypertensive agents: Commonly used antihypertensive agents (e.g. alpha blockers, diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

Amlodipine
Simvastatin: Co-administration of simvastatin with multiple doses of amlodipine increases exposure to simvastatin compared to when simvastatin is administered alone. It is recommended that the dose of simvastatin be reduced to an appropriate dose in accordance with the Product Information of simvastatin for patients concomitantly on amlodipine.

CYP3A4 inhibitors: A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50% and the effect of amlodipine is increased). The possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded. Caution should therefore be exercised when co-administering amlodipine with CYP3A4 inhibitors.
CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, hypericum perforatum [St John's Wort]): Co-administration may lead to reduced plasma concentrations of amlodipine. Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal.
In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin (glyceryl trinitrate), digoxin, warfarin, atorvastatin, aluminium/magnesium antacid, cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, ethanol and oral hypoglycaemic drugs.

Cyclosporin: The pharmacokinetics of cyclosporin were not altered when cyclosporin was coadministered with amlodipine in renal transplant patients. The patients were not taking corticosteroids.

Grapefruit juice: Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers. Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Sildenafil: A single 100 mg dose of sildenafil in 16 patients with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Dantrolene (infusion): Due to risk of hyperkalaemia, it is recommended that the concomitant administration of calcium channel blockers such as amlodipine with intravenous dantrolene be avoided in patients susceptible to malignant hyperthermia, and in the management of malignant hyperthermia.

Valsartan

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further with Zetakardoval.

Potassium: Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) requires caution and frequent monitoring of potassium levels.

Hepatic Transporters: Co-administration with inhibitors of the hepatic uptake transporter OATP1B1 (such as rifampicin, cyclosporin) or hepatic efflux transporter MRP2 (e.g. ritonavir) may increase the systemic exposure to valsartan.

Dual blockade of the renin-angiotensin system (RAS) with ARBs, ACEIs or aliskiren:
The concomitant use of ARBs, including valsartan, with other agents acting on the RAS is associated with an increased incidence of hypotension, hyperkalaemia, and changes in renal function compared to therapy with one RAS blocker. It is recommended to monitor blood pressure, renal function and electrolytes in patients on Zetakardoval and other agents that affect the RAS (see "Precautions").

The concomitant use of ARBs including valsartan, or ACEIs, with aliskiren is contraindicated in patients with Type 2 diabetes mellitus (see "Contraindications").

Combination use of ACE inhibitors or angiotensin receptor antagonist, thiazide diuretics and anti-inflammatory drugs (NSAIDs or COX-2 inhibitors): When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, the use of an ACE inhibiting drug (ACE-inhibitors) or angiotensin receptor antagonist, a thiazide diuretic (including hydrochlorothiazide) and an anti-inflammatory drug (NSAID or COX-2 inhibitor) at the same time increase the risk of renal impairment. Concomitant use of angiotensin II antagonists and NSAIDs in patients who are elderly, volume-depleted (including those on diuretic therapy) or have compromised renal function may lead to an increased risk of worsening renal function, including possible acute renal failure. This includes use in fixed combination products containing more than one class of drug. Combined use of these medications

should be accompanied by increased monitoring of serum creatinine, particularly when initiating or modifying treatment.

In monotherapy with valsartan: no drug interactions of clinical significance have been found with the following drugs: cimetidine, warfarin, frusemide, digoxin, atenolol, indomethacin hydrochlorothiazide, amlodipine, glibenclamide.

As valsartan is not metabolised to a significant extent, clinically relevant drug-drug interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are not expected with valsartan. Although valsartan is highly bound to plasma proteins, *in vitro* studies have not shown any interaction at this level with a range of molecules which are also highly protein-bound, such as diclofenac, frusemide, and warfarin.

Adverse Effects

Adverse Reactions with Suspected Relationship to Zetakardoval
Adverse drug reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Infections and infestations	
Common:	Nasopharyngitis, influenza
Immune system disorders	
Rare:	Hypersensitivity
Metabolism and nutrition disorders	
Uncommon:	Anorexia, hypercalcemia, hyperlipidaemia, hyperuricaemia, hypokalemia, hyponatremia
Eye disorders	
Rare:	Visual disturbance
Psychiatric disorders	
Rare:	Anxiety
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, somnolence, dizziness postural, paraesthesia, coordination abnormal
Ear and labyrinth disorders	
Uncommon:	Vertigo
Rare:	Tinnitus
Cardiac disorders	
Uncommon:	Tachycardia, palpitations
Rare:	Syncope
Vascular disorders	
Uncommon:	Orthostatic hypotension
Rare:	Hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Cough, pharyngolaryngeal pain
Gastrointestinal disorders	
Uncommon:	Diarrhea, nausea, abdominal pain, constipation, dry

	mouth
Skin and subcutaneous tissue disorders	
Uncommon:	Rash, erythema
Rare:	Hyperhidrosis, exanthema, pruritus
Muscleoskeletal and connective tissue disorder	
Uncommon:	Joint swelling, back pain, arthralgia
Rare:	Muscle spasm, sensation of heaviness
Renal and urinary disorders	
Rare:	Pollakiuria, polyuria
Reproductive system and breast disorders	
Rare:	Erectile dysfunction
General disorders and administration site conditions	
Common:	Oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthemia, hot flush

Additional Information on the Combination

Peripheral oedema, a recognised side effect of amlodipine, was generally observed at a lower incidence in patients who received the amlodipine/valsartan combination than in those who received amlodipine alone.

Laboratory Evaluation

Very few hypertensive patients treated with amlodipine/valsartan showed notable changes in laboratory test results from baseline. There was a slightly higher incidence of notably increased blood urea nitrogen in the amlodipine/valsartan (5.5 %) and valsartan monotherapy (5.5%) groups as compared to the placebo group (4.7%).

Additional Information on Individual Components

Adverse reactions previously reported with one of the individual components may occur with Zetakardoval even if not observed in clinical trials.

Amlodipine

Other additional adverse experiences reported in clinical trials and post marketing reports with amlodipine monotherapy, irrespective of their causal association with the study drug, were as follows:
The most commonly observed adverse event was vomiting.

Less commonly observed adverse events were peripheral ischaemia, alopecia, anorexia, altered bowel habits, dyspepsia, dysphagia, flatulence, dyspnoea, epistaxis, rhinitis, gastritis, gingival hyperplasia, gynaecomastia, hyperglycaemia, impotence, increased urinary frequency, malaise, sexual dysfunction, insomnia, nervousness, depression, abnormal dreams, depersonalisation, mood changes, pain, rigors, weigh gain, arthrosis, muscle cramps, myalgia, hypoesthesia, dysgeusia, tremor, peripheral neuropathy, pancreatitis, leucopenia, thrombocytopenia, purpura, vasculitis, conjunctivitis, diplopia, eye pain, photosensitivity, micturition frequency and disorder, nocturia, sweating increased, thirst, angioedema and erythema multiforme.

Rarely observed adverse events were cardiac failure, pulse irregularity, extrasystoles, skin discolouration, urticaria, skin dryness, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, increased appetite, loose stools, coughing, dysuria, parosmia, tast perversion, xerophthalmia and weight decrease.

As with other calcium channel blockers the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: myocardial infarction, angina,

arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), chest pain, Stevens-Johnson syndrome, allergic reactions.

There have been infrequent, post marketing reports of hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis). Some cases severe enough to require hospitalisation have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

Exceptional cases of extrapyramidal syndrome have been reported.

In a long-term placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Risk of Myocardial Infarction or Increased Angina: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. Arrhythmia (including ventricular tachycardia and atrial fibrillation) has also been reported with calcium channel blocker therapy. These adverse events may not be distinguishable from the natural history of the underlying disease.

Valsartan

Other additional adverse experiences reported in clinical trials and post marketing reports with valsartan monotherapy in the hypertension indication, irrespective of their causal association with the study drug, were as follows:
Viral infections, upper respiratory infections, pharyngitis, sinusitis, rhinitis, neutropenia, thrombocytopenia, insomnia, libido decrease, myalgia, dyspepsia, flatulence, muscle cramps, chest pain, anorexia, vomiting, dyspnoea, elevated liver enzymes and very rare reports of hepatitis. Altered renal function (especially in patients treated with diuretics or in patients with renal impairment), acute renal failure, renal insufficiency, angioedema and hypersensitivity (vasculitis, serum sickness) can occur.

Laboratory Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of valsartan.
Creatinine: Minor elevations in creatinine occurred in 0.8% of patients taking valsartan and 0.6% given placebo in controlled trials of hypertensive patients. In heart failure patients, increases in serum creatinine greater than 50% were observed in 3.9% of valsartan treated patients compared to 0.9% of placebo treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients, 4.8% of valsartan plus captopril-treated patients, and 3.4% of captopril-treated patients.
Blood urea nitrogen: In heart failure trials, increases in blood urea nitrogen (BUN) greater than 50% were observed in 16.6% of patients treated with valsartan compared to 6.3% of patients treated with placebo.
Haematocrit and haemoglobin: Greater than 20% decreases in haemoglobin and haematocrit were observed in 0.4% and 0.8% respectively, of valsartan patients compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anaemia.
Liver function tests: Occasional elevations (greater than 150%) of liver function values were reported in patients treated with valsartan. Three patients (< 0.1%) treated with valsartan discontinued treatment for elevated liver function values. Elevated liver enzymes have also been reported in post-marketing surveillance.
Neutropenia: Neutropenia was observed in 1.9% of patients treated with valsartan and 0.8% of patients treated with placebo.

Zetakardoval is not recommended for use in patients aged below 18 years due to a lack of safety and efficacy data.

Patients with renal and hepatic impairment

No dosage adjustment is required for patients with mild to moderate renal impairment but caution should be exercised when administering Zetakardoval to patients with hepatic impairment or biliary obstructive disorders (see **Precautions**). Monitoring of creatinine and potassium levels is advised for patients with moderate renal impairment. Liver function should be monitored in patients with mild to moderate hepatic impairment .The daily dose of Zetakardoval should not exceed 5/80 mg in patients with mild to moderate hepatic impairment without cholestasis. Zetakardoval is contraindicated in severe hepatic and renal impairment and patients undergoing dialysis.

Overdosage

Symptoms

There is no experience of overdose with Zetakardoval yet. Overdose with valsartan may result in pronounced hypotension with dizziness which could lead to depressed level of consciousness, circulatory collapse and/or shock. Overdose with amlodipine may result in excessive peripheral vasodilation with marked hypotension and possibly reflex tachycardia. Dysrhythmias may occur following overdose with any calcium antagonists. Hypotension and bradycardia are usually seen within one to five hours following overdose. Hypotension can persist for longer than 24 hours despite treatment. Cardiac rhythm disturbances have been noted to persist for up to seven days. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to Zetakardoval overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. If the ingestion is recent, induction of vomiting or gastric lavage may be considered. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Both valsartan and amlodipine are unlikely to be removed by haemodialysis.

Presentation and Storage Conditions

Zetakardoval 5/160 (5mg amlodipine and 160mg valsartan): Pink round biconvex film coated tablets.
Zetakardoval 10/160 (10mg amlodipine and 160mg valsartan): Green round biconvex film coated tablet.
Zetakardoval 5/320 (5mg amlodipine and 320mg valsartan): Yellow oblong film coated tablet.
Zetakardoval 10/320 (10mg amlodipine and 320mg valsartan): Grey oblong scored film coated tablet.

Package:

Zetakardoval 5/160: Carton Box containing 1, 2 or 3 (Al/Al) strips, each containing 5 film coated tablets + insert leaflets.
Zetakardoval 10/160: Carton Box containing 1, 2 or 3 (Al/Al) strips, each containing 5 film coated tablets + insert leaflets.
Zetakardoval 5/320: Carton Box containing 1, 2 or 3 (Al/PVDC) strips, each containing 5 film coated tablets + insert leaflets.
Zetakardoval 10/320: Carton Box containing 1, 2 or 3 (Al/PVDC) strips, each containing 5 film coated tablets + insert leaflets.

Serum potassium: In patients with hypertension, increases in serum potassium greater than 20% were observed in 4.4% of patients treated with valsartan compared to 2.9% of placebo-treated patients. No patients treated with valsartan discontinued therapy for hyperkalaemia. In heart failure patients, increases in serum potassium greater than 20% were observed in 10.0% of valsartan treated patients compared to 5.1% of placebo treated patients.

Post-marketing Experience

Amlodipine

Gynaecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalisation, have been reported in association with use of amlodipine.

Valsartan

The following additional adverse reactions have been reported in post-marketing experience with valsartan:
Blood and Lymphatic: There are very rare reports of thrombocytopenia.
Hypersensitivity: There are rare reports of angioedema.
Digestive: Elevated liver enzymes and very rare reports of hepatitis.
Renal: Impaired renal function.
Clinical Laboratory Tests: Hyperkalemia.
Dermatologic: Alopecia.
Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.
Dermatitis bullous and hyponatraemia of unknown incidence have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to:

- Egyptian Pharmacovigilance Center (EPVC) at: www.epvc.gov.eg
- Zeta Pharma for Pharmaceutical Industries (Pharmacovigilance department):
  - ✓ E-mail: pv@zeta-pharma.com
  - ✓ Zeta Pharma Website: https://www.zetapharma.net/en/patient-supports
  - ✓ Mobile: +2 01002355526
  - ✓ Telephone: +2 0222715582
  - ✓ Fax: +2 0222715583

Dosage and Administration

The recommended dose is one tablet per day of either Zetakardoval 5/160 mg, 10/160 mg, 5/320 mg or 10/320 mg. Both amlodipine and valsartan monotherapy can be taken with or without food. Zetakardoval should be consistently taken with or without food. It is recommended to take Zetakardoval with some water

For convenience, patients adequately controlled on valsartan and amlodipine may be switched to Zetakardoval containing the same component doses from separate tablets. A patient whose blood pressure i not adequately controlled on amlodipine or valsartan monotherapy may be switched to combination therapy with Zetakardoval 5/160, 10/160, 5/320 and 10/320 mg. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

The elderly

Caution is advised when increasing the dose in elderly patients (see **Pharmacokinetics**).

Children and adolescents

Storage: Store at temperature not exceeding 30°C in a dry place.

Manufactured by Adwia for Zeta Pharma for Pharmaceutical Industries

زيتاكاردوڤال

أقراص مغلفة

٥/١٦٠ ، ٥/٣٢٠ ، ١٠/١٦٠ ، ١٠/٣٢٠

لا يستخدم أثناء الحمل حيث أنه يسبب إصابة أو وفاة الجنين

هذه النشرة تجيب على بعض الأسئلة الشائعة حول زيتاكاردوڤال.

هذه النشرة لا تحتوي على جميع المعلومات المتاحة. لذلك فإنه لابد من التحدث إلى طبيبك أو الصيدلي.

إذا كان لديك أي مخاوف حول أخذ هذا الدواء، اسأل طبيبك أو الصيدلي.

احتفظ بهذه النشرة مع الدواء.

قد تحتاج إلى قراءته مرة أخرى.

فيم يستخدم زيتاكاردوڤال؟

يتم استخدام زيتاكاردوڤال للسيطرة على ارتفاع ضغط الدم.

كل شخص لديه ضغط دم. هذا الضغط يساعد الدم على الانتشار حول جسمك. قد يكون الضغط مختلفًا في الاوقات المختلفة من اليوم، اعتمادا على كيفية انشغالك أو قلقك. يكون لديك ارتفاع ضغط الدم عندما يبقى ضغط الدم أعلى مما هو مطلوب، حتى عندما تكون هادئا ومرتاحا.

ارتفاع ضغط الدم يزيد من عبء العمل على القلب والأوعية الدموية. إذا استمر لفترة طويلة من الوقت، فإنه يمكن أن يلحق الضرر بالأوعية الدموية في الدماغ والقلب والكلى. هذا يمكن أن يؤدي إلى السكتة الدماغية أو فشل القلب أو الفشل الكلوي. ارتفاع ضغط الدم يزيد من خطر الإصابة بالنوبات القلبية. خفض ضغط الدم يقلل من فرصة حدوث هذه الاضطرابات.

زيتاكاردوڤال يحتوي على فالسارتان وأملودبين بيسلات. هذه الأدوية تخفض ضغط الدم بطريقتان مختلفتان.

١. فالسارتان يمنع تأثير أنجيوتنسين II، وهو مادة في الجسم تقوم بتضييق الأوعية الدموية وتجعل ضغط الدم يرتفع. عندما يمنع تأثير الأنجيوتنسين II، تسترخي الأوعية الدموية وينخفض ضغط دمك.

٢. أملودبين بيسلات يمنع حركة الكالسيوم إلى خلايا القلب والأوعية الدموية. ونتيجة لذلك، تسترخي الأوعية الدموية ويزداد توريد الدم والأكسجين إلى القلب مع تقليل عبء العمل.

يستخدم زيتاكاردوڤال لعلاج ضغط الدم المرتفع في المرضى الذين لا يمكن التحكم في ضغط الدم بما فيه الكفاية مع إما أملودبين أو فالسارتان على حدى.

اسأل طبيبك إذا كان لديك أي أسئلة حول لماذا هذا الدواء قد وصف لك.

قد يكون طبيبك قد وصفه لغرض آخر.

لا توجد معلومات كافية حول استخدام زيتاكاردوڤال في الاطفال.

هذا الدواء متاح فقط مع وصفة الطبيب. إنه ليس ادمان.

وزارة الصحة
تسجيل الأدوية
نشرة معتمدة
صيدلية

قبل أن تأخذ زيتاكاردوڤال

متى يجب ان لا تأخذ زيتاكاردوڤال

لا تأخذ زيتاكاردوڤال إذا كان لديك في أي وقت مضى رد فعل تحسسي بعد اخذ:

- فالسارتان أواملودبين بيسلات (المكونات النشطة في زيتاكاردوڤال)
- الأدوية التابعة لمجموعة من المواد الكيميائية تسمى dihydropyridines، وتستخدم لعلاج ضغط الدم ومشاكل القلب الأخرى.
- أي من المكونات الأخرى المذكورة في نهاية هذه النشرة.

أعراض الحساسية قد تشمل ضيق في التنفس، الصفير أو صعوبة في التنفس؛ تورم في الوجه أو الشفاه أو اللسان أو أجزاء أخرى من الجسم؛ طفح جلدي، حكة أو خلايا النحل على الجلد.

لا تأخذ زيتاكاردوڤال إذا كنت حامل أو تنوي أن تصبحي حامل.

لا ينصح استخدام زيتاكاردوڤال في الحمل. مثل غيرها من الأدوية المماثلة، فإنه يمكن أن تؤثر على طفلك الذي لم يولد بعد.

لا تأخذ زيتاكاردوڤال إذا كان لديك أي من الظروف الطبية التالية:

- أمراض الكلى الشديدة أو حدوث غسيل الكلى
- أمراض الكبد الشديدة بما في ذلك تليف الكبد الصفراوي
- الكولستاس، وهو تقليل أو توقف تدفق الصفراء

لا تأخذ زيتاكاردوڤال إذا كنت تأخذ أدوية خفض ضغط الدم الأخرى التي تحتوي على aliskiren وتعاني من النوع الثاني من مرض السكري.

لا تأخذ زيتاكاردوڤال بعد تاريخ انتهاء الصلاحية المطبوع على العلبة أو إذا كانت التعبئة والتغليف ممزقة أو يظهر بها علامات العبث.

في هذه الحالة، قم بإعادته إلى الصيدلي.

قبل أن تبدأ في أخذه أخبر طبيبك إذا كان لديك / كان لديك أي من المشاكل الصحية التالية / الظروف الطبية:

- مشاكل في الكلى أو تلقى عملية زرع كلية
- مشاكل في الكبد
- مشاكل في القلب، بما في ذلك عرقلة تدفق الدم من تضييق الصمامات (تضيق) أو الحاجز الموسع (HOCM)
- حالة تعرف باسم أولية فرط الالدووستيرون (متلازمة كوون)، اضطراب هرموني يسبب احتباس السوائل
- تورم، من الوجه و الحلق بشكل أساسي، حين أخذ الأدوية الأخرى (بما في ذلك مثبطات ACE أو aliskiren)
- يعاني من عدة حلقات من القيء أو الإسهال أو يأخذ مدر للبول (دواء يزيد كمية البول).

قد يرغب طبيبك في أخذ احتياطات خاصة إذا كان لديك أي من الظروف أعلاه.

أخبري طبيبك إذا كنتي تقومين بالرضاعة الطبيعية. اسأل طبيبك حول مخاطر وفوائد أخذ زيتاكاردوڤال في هذه الحالة.

من غير المعروف ما إذا كان فالسارتان أو أملودبين - المكونات النشطة لل زيتاكاردوڤال- تمر إلى حليب الثدي ويمكن أن تؤثر على طفلك.

أخبر طبيبك إذا كنت تعاني من الحساسية إلى أي أدوية أخرى، وأطعمة، والأصباغ أو المواد الحافظة.

طبيبك سوف ترغب في معرفة ما إذا كنت عرضة للحساسية.

إذا لم تكن قد أخبرت طبيبك حول أي من هذه الأشياء، قل له / لها قبل أن تأخذ زيتاكاردوڤال.

تناول أدوية أخرى

أخبر طبيبك أو الصيدلي إذا كنت تأخذ أي أدوية أخرى، بما في ذلك الأدوية التي تشتريها دون وصفة طبية من صيدلية، سوبر ماركت أو متجر للأغذية الصحية.

بعض الأدوية وزيتاكاردوفال قد تتداخل مع بعضها البعض. قد يحتاج الطبيب إلى تغيير الجرعة أو اتخاذ احتياطات أخرى. في بعض الحالات التي قد تضطر إلى التوقف عن اخذ واحد من الأدوية. هذا ينطبق خاصة للأدوية المذكورة ادناه.

وتشمل ما يلي:

• الأدوية المستخدمة لعلاج ارتفاع ضغط الدم وبعض أمراض القلب الاخرى بما في ذلك الأقراص السائلة أو الأدوية المدرة للبول، مثبطات ACE، أليسبيرين و حاصرات بيتا.

• سمفاستاتين (دواء يستخدم ليساعد على خفض مستويات الكوليسترول في الدم)، قد تضطر إلى خفض الجرعة عند اخذها مع زيتاكاردوفال

• بعض المضادات الحيوية (ريفامبيسين)، الأدوية المضادة للرفض (السيكلوسبورين)، مضادات الفيروسات القهقرية (ريتونافير) التي قد تزيد من تأثير فالسارتان

• أقراص أو مستحضرات أو المكملات الغذائية التي تزيد من مستويات البوتاسيوم في الدم (مثل أنواع معينة من مدرات البول، مكملات البوتاسيوم وبدائل الملح الخ) ، والليثيوم (دواء يستخدم لعلاج بعض انواع الاكتئاب)

• العوامل المضادة للاختلاج (على سبيل المثال. كاربامازيبين، فينوباربيتال، الفينيتوين، فوسفينيتين، بريميدون)، ريفامبيسين، نبتة سانت جونز.

• النيتروجلسرين والنترات الأخرى، أو مواد أخرى تسمى "موسعات"

• الأدوية المستخدمة في فيروس نقص المناعة البشرية/الإيدز (على سبيل المثال ريتونافير) أو لعلاج الالتهابات الفطرية (على سبيل المثال. كيتوكونازول)

• أنواع معينة من مسكنات الألم تسمى الأدوية غير الستيرويدية المضادة للالتهابات أو مثبطات السيكلوأكسجيناز-٢ الانتقائية (مثبطات كوكس-٢).

• الدانترول ين في الوريد تستخدم ل علاج ارتفاع الحرارة الخبيثة.

قد يتحقق طبيبك أيضًا من وظائف الكلى.

طبيبك والصيدلي لديهم قائمة أكثر اكتمالا من الأدوية لتكون حريصا حين أخذ زيتاكاردوفال.

كيفية اخذ زيتاكاردوفال

اتبع بعناية جميع التوجيهات التي اعطيت لك من قبل طبيبك و الصيدلي.

قد تختلف هذه التعليمات عن المعلومات الواردة في هذا النشره.

إذا كنت لا تفهم التعليمات في النشرة، اسأل طبيبك أو الصيدلي للحصول على مساعدة.

كم تأخذ

سيخبرك طبيبك كم عدد أقراص التي تأخذها كل يوم. الجرعة المعتادة هي قرص واحد في اليوم.

اعتمادًا على كيفية استجابتك العلاج، قد يقترح طبيبك جرعة أعلى أو أقل.

متى تأخذها

خذ جرعة زيتاكاردوفال الخاصة بك في نفس الوقت كل يوم. وهذا يساعدك أيضا على تذكر أن تأخذها ، وخاصة إذا كنت أعتبر كجزء من روتينك المعتاد (على سبيل المثال في وقت وجبة الإفطار). هذا الدواء سوف يعمل طوال ٢٤ ساعة حتى الجرعة التالية المستحقة.

كيفية أخذها

ابتلع القرص مع كوب كامل من الماء.

قم بأخذ زيتاكاردوفال دائما بنفس الطريقة، مع أو بدون طعام.

يمكنك أن تأخذه مع أو بدون طعام لكنه سيعمل بشكل أفضل إذا كنت دائما تأخذه بنفس الطريقة كل يوم.

كم من الوقت لأخذه

خذ هذا الدواء حتى يقول لك الطبيب أن تتوقف حتى لو كنت تشعر أنك بصحة جيده. الأشخاص الذين يعانون من ارتفاع ضغط الدم غالبا ما يشعرون انهم بصحة جيده ولا يلاحظون أي علامات من هذه المشكلة.

إذا نسيت أن تأخذها

إذا كان الوقت قد حان تقريبا للجرعة المقبلة، تخطي الجرعة الفائتة وخذ التالية في وقتها.

خلاف ذلك، تأخذ الجرعة في أقرب وقت تتذكر ثم تعود إلى أخذها كما تفعل عادة.

لا تأخذ جرعة مزدوجة لتعويض تلك التي فاتتك. هذا قد يزيد من فرص الاثار الجانبية.

إذا كان لديك مشكلة في التذكر متى تأخذ دوائك، اسأل الصيدلي الخاص بك لبعض التلميحات.

إذا كنت تأخذ الكثير (جرعة زائدة)

اتصل هاتفيًا على الفور بطبيبك أو مركز معلومات السموم لـ المشورة ، أو الذهاب إلى الطوارئ في أقرب مستشفى إذا كنت تعتقد أنك أو أي شخص آخر قد اخذت الكثير من زيتاكاردوفال. افعل ذلك حتى لو لا توجد علامات على عدم الراحة أو التسمم. الاحتفاظ بارقام الهاتف لهذه الأماكن مفيد.

الكثير من زيتاكاردوفال قد تجعلك يشعر بالدوار، رأس خفيف او إغماء. قد تواجه تنفس سريع، صُحل أو برودة في الجلد، تكون نبضات القلب أسرع من المعتاد. وذلك لأن ضغط الدم منخفض جدا.

وقتما تأخذ زيتاكاردوفال

أشياء يجب عليك القيام بها

إذا أصبحتي حاملاً أثناء أخذ زيتاكاردوفال، أخبري طبيبك فورا.

يجب أن لا تأخذي هذا الدواء بينما أنت حامل.

أخبر طبيبك إذا، لأي سبب من الأسباب، لم تكن قد اتخذت الدواء الخاص بك تماما كما هو مقرر. وإلا قد يعتقد طبيبك أنه لم يكن فعالا ويقوم بتغيير العلاج الخاص بك دون داع.

تأكد من الحفاظ على جميع مواعيد طبيبك بحيث يمكن التحقق من تقدم حالتك. عليك القيام بذلك حتى لو كنت تشعر أنك بخير.

الأشخاص الذين يعانون من ارتفاع ضغط الدم في كثير من الأحيان لا يلاحظون أي علامات لهذه المشكله. ولكن من المهم الحفاظ على تتبع تقدم حالتك. طبيبك سوف يرغب في التحقق من ضغط دمك ووظائفالكلى والكبد من وقت لآخر.

إذا كنت ستخضع لعملية جراحية أخبر طبيبك وطبيب التخدير أنك تأخذ زيتاكاردوفال.

زيتاكاردوفال قد يؤثر على بعض الأدوية التي تتلقاها خلال الجراحه.

إذا كنت على وشك أن تبدأ على أي دواء جديد، ذكر طبيبك والصيدلي انك تأخذ زيتاكاردوفال.

أخبر أي طبيب آخر أو طبيب أسنان أو الصيدلي الذي يعاملك أنك تأخذ زيتاكاردوفال.

أشياء يجب عليك عدم القيام بها

لا تستخدم زيتاكاردوفال لعلاج أي شكاوى أخرى ما لم يقول الطبيب أنه يمكنك ذلك.

لا تعطي هذا الدواء لأي شخص آخر، حتى لو كانت حالتهم تبدو أنها مشابهة لك.

أشياء يجب توخي الحذر منها

تجنب تناول الجريب فروت أو شرب عصير الجريب فروت. عصير الجريب فروت يمكن أن يؤثر على التمثيل الغذائي لبعض الأدوية، بما في ذلك أملودبين.

كن حذرا أثناء القيادة، تشغيل الآلات أو القيام بالوظائف التي تتطلب منك أن تكون في حالة تأهب أثناء اتخاذ زيتاكاردوفال حتى تعرف كيف يؤثر عليك.

هذا الدواء يمكن أن يسبب التعب، النعاس أو الدوخة في بعض الأشخاص. إذا كان لديك هذه الأعراض، لا تقود أو تفعل أي شيء آخر يمكن أن يكون خطير.

إذا كان هذا الدواء يجعلك تشعر بالدوار أو رأس خفيف، توخى الحذر عند النهوض من وضع الجلوس أو النوم. يمكن عادة منع الدوخة عن طريق القيام ببطء وثني عضلات الساق والاصابع للحصول على تتدفق الدم. عندما تخرج من السرير تتدلى ساقيك على الجانب ل دقيقة أو اثنتين قبل الوقوف.

الآثار الجانبية

أخبر طبيبك أو الصيدلي في أقرب وقت ممكن إذا كنت لا تشعر أنك جيد أثناء اتخاذك ل زيتاكاردوفال، حتى لو كنت لا تعتقد أنه مرتبط بهذا الدواء.

جميع الأدوية يمكن أن يكون لها آثار جانبية. في بعض الأحيان تكون خطيرة ، ولكن معظم الوقت ليسوا كذلك. يمكن ان تحتاج إلى علاج طبي إذا كنت تعاني بعض الآثار الجانبية. لا تنزعج من هذه القائمة من الآثار الجانبية المحتملة. من الممكن الا يحدث لك أيا منها. اطلب من طبيبك أو الصيدلي الإجابة على أي أسئلة قد تكون لديك.

أخبر طبيبك إذا لاحظت أي من هذه الآثار الجانبية والتي قد تقلقك:

- صداع
- أزيز، صفير، رنين أو الضوضاء المستمرة الأخرى في الأذنين
- الدوخة، والإحساس الغزل، التغيرات في الرؤية، حركات غير منسقة
- الدوخة على الوقوف، خاصة عند القيام من وضع الجلوس او النوم
- النعاس والتعب والضعف أو صعوبة النوم
- ألم في الظهر أو المفاصل
- ألم العضلات، وألم أو ضعف العضلات، تشنجات
- سيلان الأنف أو الجيوب الأنفية المزدحمة
- السعال الجاف أو التهاب الحلق أو أجش صوت
- جفاف الفم
- نزيف أو ضعف أو لثة متضخمة
- اضطراب في المعدة، والألم، والإسهال أو الامساك

- الغثيان (الشعور بالمرض) أو القيء
- وخز أو خدر في اليدين أو اقدام
- طفح جلدي أو احمرار أو تقرحات أو تقشير الجلد، والحكة
- التعرق المفرط
- الشعور بالقلق أو الحزن
- مشاكل في الوظيفة الجنسية
- تكبير الثدي في الرجال
- تساقط الشعر أو ترقق غير عادي
- تمرير البول أكثر من المعتاد أو الرغبة المتكررة في التبول
- احمرار وشعور دافئ من الوجه و / أو الرقبة
- تورم الكاحلين والقدمين والوجه أو الأيدي
- التنظيف
- خفقان
- عسر الهضم
- التعب غير العادي أو الضعف
- زيادة الوزن
- الشعور بالتوتر أو الاكتئاب أو تغير الحالة المزاجية
- إحساس مشوه بالذوق
- حساسية للضوء

أخبر طبيبك على الفور أو اذهب إلى الحوادث والطوارئ في أقرب مستشفى إذا لاحظت أي مما يلي:

- علامات الحساسية مثل الطفح الجلدي، الحكة أو خلايا النحل على الجلد. تورم في الوجه والشفاه واللسان أو أجزاء أخرى من الجسم؛ ضيق في التنفس، صفير أو التنفس المضطرب
- الشعور بنبض القلب السريع أو غير المنتظم (قصف ، سباق ، تخطي دقات)
- ألم في الصدر
- التعب أو نقص الطاقة، وضيق في التنفس عند ممارسة الرياضة
- نزيف أو كدمات بسهولة أكبر من المعتاد
- أعراض ثابتة "تشبه الإنفلونزا" مثل القشعريرة والحمى والتهاب الحلق، ألم المفاصل، القروح في الفم، تضخم الغدد
- الدوخة الشديدة أو الإغماء
- ألم في المعدة مع الغثيان، القيء، وفقدان الشهية، والشعور عموما بأنك لست جيدا، والحمى، والحكة، اصفرار الجلد والعينين، والبول الداكن اللون

القائمة أعلاه تشمل الجانب خطيرة الآثار التي قد تتطلب الاهتمام الطبي. هذه الآثار الجانبية لاتحدث بشكل متكرر.

أخبر طبيبك إذا لاحظت أي شيء آخر يجعلك تشعر أنك لست جيدا.

الآثار الجانبية الأخرى غير المذكورة أعلاه قد تحدث أيضا في بعض الناس.

الإبلاغ عن الآثار الجانبية

إذا كنت تعاني من أي آثار جانبية ، فتحدث إلى طبيبك أو الصيدلي أو الممرض. يتضمن ذلك أي آثار جانبية محتملة غير مدرجة في هذه النشرة. يمكنك أيضًا الإبلاغ عن الآثار الجانبية مباشرةً عن طريق :

- المركز المصري لليقظة الدوائية عن طريق الموقع الألكتروني : www.epvc.gov.eg
- شركة زيتفارم للصناعات الدوائية (قسم اليقظة الدوائية):
  - ✓ البريد الألكتروني: pv@zeta-pharma.com
  - ✓ الموقع الإلكتروني: https://www.zetapharma.net/en/patient-supports
  - ✓ موبايل: ٠١٠٠٢٣٥٥٥٢٦
  - ✓ تليفون: ٠٢٢٢٧١٥٥٨٢
  - ✓ فاكس: ٠٢٢٢٧١٥٥٨٣

بعد استخدام زيتاكاردوفال

تخزين

- حافظ على الأقراص الخاصة بك في العلبة الأصلية حتى يحين الوقت لاخذهم.
- قم بتخزينها في مكان جاف بارد أقل من ٣٠ درجة منوية (درجة حرارة الغرفة).
- لا تخزن زيتاكاردوفال أو أي أدوية أخرى في الحمام أو بالقرب من الحوض.
- لا تترك زيتاكاردوفال في سيارة أو على عتبة نافذة.

الحرارة والرطوبة يمكن أن تدمر بعض الادويه. زيتاكاردوفال سوف يبقي جيدا إذا كان باردا وجافا.

الاحتفاظ بالأدوية حيث لا يمكن للأطفال الوصول إليهم. خزانة مقفلة على الأقل واحد ونصف متر فوق سطح الأرض هو مكان جيد لتخزين الأدوية.

التخلص

إذا أخبرك طبيبك بالتوقف عن أخذ زيتاكاردوفال، أو أنه قد مرت تاريخ انتهاء صلاحيته، اسأل الصيدلي ما يجب القيام به مع أي أقراص متبقية.

وصف المنتج

كيف يبدو

زيتاكاردوفال ١٦٠/٥ (٥ مجم أملودبين و ١٦٠ مجم فالسارتان): أقراص مغلفة مستديرة محدبة الوجهين زهرية اللون.
زيتاكاردوفال ٣٢٠/٥ (٥ مجم أملودبين و ٣٢٠ مجم فالسارتان): أقراص مغلفة مستطيلة صفراء اللون.
زيتاكاردوفال ١٦٠/١٠ (١٠ مجم أملودبين و ١٦٠ مجم فالسارتان): أقراص مغلفة مستديرة محدبة الوجهين خضراء اللون.
زيتاكاردوفال ٣٢٠/١٠ (١٠ مجم أملودبين و ٣٢٠ مجم فالسارتان): أقراص مغلفة مستطيلة قابلة للتقسيم رمادية اللون.

العبوة:

زيتاكاردوفال ١٦٠/٥: عبوة كرتون تحتوي على ١،٢،٣ (Al/Al) شرائط كل شريط يحتوي على ٥ أقراص مغلفة + نشرة داخلية.
زيتاكاردوفال ٣٢٠/٥: عبوة كرتون تحتوي على ١،٢،٣ (Al/PVDC) شرائط، كل شريط يحتوي على ٥ أقراص مغلفة + نشرة داخلية.
زيتاكاردوفال ١٦٠/١٠: عبوة كرتون تحتوي على ١،٢،٣ (Al/Al) شرائط، كل شريط يحتوي على ٥ أقراص مغلفة + نشرة داخلية.

زيتاكاردوفال ٣٢٠/١٠: عبوة كرتون تحتوي على ١،٢،٣ (Al/PVDC) شرائط كل شريط يحتوي على ٥ أقراص مغلفة + نشرة داخلية.

المكونات:

زيتاكاردوفال ١٦٠/٥:

المواد الفعالة: أملودبين بيسلات، فالسارتان

المواد غير الفعالة: سيلاكتوز، بولي بلاسدون، PVP، ايرسول، ماغنسيوم ستيرات، أوبادراي زهري.

زيتاكاردوفال ٣٢٠/٥:

المواد الفعالة: أملودبين بيسلات، فالسارتان

المواد غير الفعالة: سيلاكتوز، بولي بلاسدون، PVP، ايرسول، ماغنسيوم ستيرات، أوبادراي أصفر.

زيتاكاردوفال ١٦٠/٥:

المواد الفعالة: أملودبين بيسلات، فالسارتان

المواد غير الفعالة: سيلاكتوز، بولي بلاسدون، PVP، ايرسول، ماغنسيوم ستيرات، أوبادراي أخضر.

زيتاكاردوفال ١٦٠/٥:

المواد الفعالة: أملودبين بيسلات، فالسارتان

المواد غير الفعالة: سيلاكتوز، بولي بلاسدون، PVP، ايرسول، ماغنسيوم ستيرات، أوبادراي رمادي.

تصنيع شركة أدويا لصالح شركة زيتا فارما للصناعات الدوائية