SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ADCO ZETOMAX CO 10/12,5 tablet
ADCO ZETOMAX CO 20/12,5 tablet
ADCO ZETOMAX CO 20/25 tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ADCO ZETOMAX CO 10/12,5 tablet contains lisinopril dihydrate (equivalent to 10 mg anhydrous lisinopril) and hydrochlorothiazide 12,5 mg.
Contains sugar (mannitol): 18,70 mg

Each ADCO ZETOMAX CO 20/12,5 tablet contains lisinopril dihydrate (equivalent to 20 mg anhydrous lisinopril) and hydrochlorothiazide 12,5 mg.
Contains sugar (mannitol): 38,30 mg

Each ADCO ZETOMAX CO 20/25 tablet contains lisinopril dihydrate (equivalent to 20 mg anhydrous lisinopril) and hydrochlorothiazide 25 mg.
Contains sugar (mannitol): 37,40 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.
ADCO ZETOMAX CO 10/12,5: Peach, round, 6 mm, uncoated, biconvex tablet without a score line. Stamped “LH” on one side.
ADCO ZETOMAX CO 20/12,5: White, round, 8 mm, uncoated, biconvex tablet with a score line. Stamped “LH” on one side.
ADCO ZETOMAX CO 20/25: Peach, round, 8 mm, uncoated, biconvex tablet with a score line. Stamped “LH” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild to moderate hypertension in patients who have been stabilised on their individual components given in the same proportions.

4.2 Posology and method of administration

The usual dosage is one tablet daily (ADCO ZETOMAX CO 10/12,5 or ADCO ZETOMAX CO 20/12,5), taken at approximately the same time each day. It is recommended that if the desired clinical effect cannot be achieved within 2 to 4 weeks with this dosage, the dosage may be increased to either one of the following:

- ADCO ZETOMAX CO 10/12,5: a maximum of two tablets, administered once daily.
- ADCO ZETOMAX CO 20/12,5: a maximum of two tablets, administered once daily.
- ADCO ZETOMAX CO 20/25: a maximum of one tablet daily.

Prior treatment with diuretics

Symptomatic hypotension may occur after the initial dose of ADCO ZETOMAX CO; this phenomenon occurs more likely in patients who are volume and/or salt depleted as a result of prior diuretic therapy. If possible, the diuretic therapy should be discontinued for 2 to 3 days prior to initiation of therapy with ADCO ZETOMAX CO; if this is not possible, lisinopril should be given alone at a low initial dose of 5 mg.

Special populations

Renal impairment

Thiazides may not be suitable diuretics for use in patients with renal impairment and are ineffective in moderate or severe renal impairment (creatinine clearance values of 30 ml/min or below).

ADCO ZETOMAX CO should not be used as initial therapy in any patient with renal insufficiency. In patients with creatinine clearance of > 30 and < 80 ml/min, ADCO ZETOMAX CO may be used, but only after titration of the individual components.

Paediatric population

Safety and efficacy in children have not been established.

Use in the elderly

There are no significant differences in the efficacy and tolerability to lisinopril and hydrochlorothiazide (as in ADCO ZETOMAX CO), when administered concomitantly, between elderly and younger hypertensive patients.

4.3 Contraindications

- Anuria
- Hypersensitivity to lisinopril dihydrate and hydrochlorothiazide or to any of the inactive ingredients of ADCO ZETOMAX CO (see section 2 and 6.1).

- Patients with a history of angioedema relating to previous treatment with an angiotensin-converting enzyme inhibitor (ACE-inhibitors) or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Patients with hereditary or idiopathic angioedema (see section 4.4).
- Hypersensitivity to other sulphonamide-derived medicines.
- Pregnancy and breastfeeding mothers (see section 4.6).
- Patients with aortic stenosis or hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 ml/min).
- Severe hepatic impairment.
- Concomitant use of fluoroquinolones with ACE inhibitors/Angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance ≤ 30 ml/min) and in elderly patients (see section 4.4).
- Bilateral renal artery stenosis or unilateral renal artery stenosis in the presence of single kidney.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with ADCO ZETOMAX CO may lead to toxic blood concentrations of lithium (see section 4.5).
- The concomitant use of ADCO ZETOMAX CO with aliskiren-containing products is contraindicated (see section 4.4 and 4.5).
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving ADCO ZETOMAX CO, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see section 4.3 and 4.6).

Should a woman contemplate pregnancy, an alternative antihypertensive medication should be used.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ADCO ZETOMAX CO and aliskiren is therefore contraindicated (see section 4.3). ADCO ZETOMAX CO should not be used concomitantly with aliskiren (see section 4.3).

Symptomatic hypotension

Symptomatic hypotension may occur in patients who has been volume depleted, e.g. by treatment with diuretics, a salt restricted diet, dialysis, or after severe diarrhoea and repeated vomiting, or has severe renin-dependant hypertension (see section 4.5 and 4.8).

Determination of serum electrolytes should be performed at appropriate intervals in such patients.

Initiation of treatment and dose adjustment should be monitored under close medical supervision in patients with an increased symptomatic hypotension. Special consideration should be given when this medication is administered to patients with ischaemic heart or cerebrovascular disease as an excessive decrease in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of 0,9 % saline. A transient hypotensive response does not warrant discontinuation of further doses.

Once effective blood volume and pressure have been stabilised, therapy at a reduced dosage may be reinstituted, or alternatively either of the components may be used appropriately as monotherapy.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with lisinopril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of lisinopril-hydrochlorothiazide may be necessary.

Electrolyte imbalance

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

Chloride deficit is generally mild and does not require treatment. Thiazides have been shown to increase the urinary excretions of magnesium, which may result in hypomagnesaemia.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including lisinopril.
Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, the combination trimethoprim/sulfamethoxazole also known as co-trimoxazole). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Renal insufficiency
Thiazides may not be suitable diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e. moderate or severe renal insufficiency).
ADCO ZETOMAX CO should not be administered to patients with a creatinine clearance < 80 ml/min until titration of the individual components has shown the need for the doses present in ADCO ZETOMAX CO.
In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have received ACE inhibitor treatment, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely to occur in patients with renal insufficiency.
Some hypertensive patients with no apparent pre-existing renal disease have developed increases in blood urea and serum creatinine when lisinopril has been given concomitantly with a diuretic. If this occurs during therapy with ADCO ZETOMAX CO, it should be discontinued. Reinstitution of therapy at a reduced dosage may be possible, or either of the components may be used alone as appropriate.

Prior diuretic therapy
The diuretic therapy should be discontinued for 2-3 days prior to initiation with lisinopril/hydrochlorothiazide. If this is not possible, treatment should be started with lisinopril alone, in a 5 mg dose.

Renal transplantation
Should not be used, since there is no experience with patients recently transplanted with a kidney.

Anaphylactoid reactions in haemodialytic patients

The use of ADCO ZETOMAX CO is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients undergoing haemodialysis procedures with certain dialysis membranes (e.g. with the high-flux membranes AN 69 and during low-density lipoproteins (LDL) apheresis with dextran sulphate) and concurrent treatment with ADCO ZETOMAX CO. Consideration to the use of a different type of dialysis membrane or a different class of antihypertensive agent should be given in these patients.

Hepatic disease

Caution should be exercised when thiazides are used in patients with hepatic impairment or progressive liver disease, as minor alterations of fluid and electrolyte balance may precipitate hepatic coma in these patients.

Patients receiving ADCO ZETOMAX CO who develop jaundice or marked elevations of hepatic enzymes should discontinue ADCO ZETOMAX CO and receive appropriate medical follow-up.

Surgery/anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, lisinopril may block angiotensin II formation secondary to compensatory renin release. Should hypotension occur, and is considered to be due to this mechanism, it can be corrected by volume expansion.

Metabolic and endocrine effects

ACE inhibitors and thiazide diuretics may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required. In diabetic patients treated with oral antidiabetic agents or insulin, glycaemia levels should be closely monitored during the first month of treatment with an ACE inhibitor. Latent diabetes mellitus may become manifest during thiazide therapy.

Decreased urinary calcium excretion caused by thiazides may result in intermittent and a slightly raised serum calcium concentration. Should marked hypercalcaemia occur, it may be evidence of underlying hyperparathyroidism. ADCO ZETOMAX CO therapy should be discontinued before carrying out tests for parathyroid function (see section 4.5).

Increased cholesterol and triglyceride levels may be a result of thiazide diuretic therapy.

Thiazide diuretics may precipitate hyperuricaemia and/or gout in certain patients. Due to the increase in urinary uric acid caused by lisinopril, hyperuricaemia may be attenuated by ADCO ZETOMAX CO, which contains both components.

Hypersensitivity/angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients with angiotensin-converting enzyme inhibitors, including lisinopril. In such cases, ADCO

ZETOMAX CO should be discontinued immediately and appropriate measures should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In instances where swelling has been confined only to the face and lips, the condition usually resolves without treatment, although antihistamines have been useful in relieving symptoms.
Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate emergency therapy should be administered promptly. This may include the administration of adrenaline and/or maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred. These patients should never receive any ADCO ZETOMAX CO again.
Patients with a history of angioedema unrelated to ADCO ZETOMAX CO therapy may be at increased risk of angioedema while receiving ADCO ZETOMAX CO (see section 4.3).
Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).
In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Race
ADCO ZETOMAX CO causes a higher rate of angioedema in black patients than in non-black patients.
As with other ACE inhibitors, lisinopril may be less effective in lowering blood pressure in black patients than in nonblack patients, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Desensitisation
Patients receiving ACE-inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. These reactions have been avoided when ACE-inhibitors were temporarily withheld but they reappeared upon inadvertent rechallenge.

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported for patients receiving ACE inhibitors.
In patients with normal renal function and no other complicating factors neutropenia occurs rarely.
Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor.
Lisinopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of

these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If lisinopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Cough

A non-productive, persistent cough has been reported with the use of ACE-inhibitors. The cough resolves after discontinuation of therapy. ACE-inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking ADCO ZETOMAX CO should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in the case of exposure, adequate protection should be advised to the patients to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations and biopsies. ADCO ZETOMAX CO should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

Fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors/ Angiotensin receptor blockers whether used separately and/or concomitantly.

Anti-doping test

The hydrochlorothiazide contained in ADCO ZETOMAX CO could produce a positive analytic result in an anti-doping test.

4.5 Interaction with other medicines and other forms of interaction

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren

When combined with other antihypertensive agents, additive falls in blood pressure may occur. Concomitant use of glyceryl trinitrate and other nitrates or other vasodilators may further reduce the blood pressure.
The combination of lisinopril with aliskiren-containing medicines should be avoided (see section 4.4).
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see section 4.3 and 4.4).

Medicine that may increase the risk of angioedema
Concomitant treatment of ACE inhibitors with mammalian target of rapamycin (mTOR) inhibitors (e.g. temsirolimus, sirolimus, everolimus) or neutral endopeptidase (NEP) inhibitors (e.g. racecadotril) or tissue plasminogen activator may increase the risk of angioedema.

Fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers
Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

Serum potassium
The decrease in potassium caused by thiazide diuretics is usually attenuated by the effect of lisinopril. The use of potassium supplements, potassium sparing agents or potassium containing salt substitutes, especially in patients with impaired renal function, may result in a significant increase in serum potassium. Should it be required to administer ADCO ZETOMAX CO concomitantly with any of these agents, caution should be exercised, and serum potassium should be monitored on a regular basis.

Lithium
The concomitant use of lithium with diuretics or ACE-inhibitors is not indicated. The renal clearance of lithium is reduced by ACE-inhibitors and diuretic agents, and a high risk of lithium toxicity exists. The prescribing information for lithium preparations should be reviewed before use of these preparations.

Torsades de pointes-inducing medicinal products

Because of the risk of hypokalaemia the concomitant administration of hydrochlorothiazide and medicinal products that induce torsades de pointes, e.g. some antiarrhythmics, some anti-psychotics and other drugs known to induce torsades de pointes, should be used with caution.

Tricyclic antidepressants/antipsychotics/anaesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further lowering of blood pressure (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAID's)
Indomethacin may decrease the antihypertensive efficacy of ADCO ZETOMAX CO. In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs (NSAID's), the co-administration of lisinopril may result in a further deterioration in renal function.
The administration of a non-steroidal anti-inflammatory medicine can reduce the diuretic, natriuretic and antihypertensive effects of diuretics in some patients.

Gold
Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

Sympathomimetics
Sympathomimetics can reduce the antihypertensive effect of ACE inhibitors.
Thiazides may decrease arterial responsiveness to noradrenaline, but not enough to preclude effectiveness of the pressor agent for therapeutic use.

Non-depolarising muscle relaxants
Thiazides may increase the responsiveness to non-depolarising skeletal muscle relaxants (e.g. tubocurarine).

Alcohol, barbiturates or narcotics
Potentiation of orthostatic hypotension caused by thiazides may occur.

Antidiabetic medicine (oral agents and insulin)
Treatment with a thiazide diuretic may impair glucose tolerance. This phenomenon appeared to be more likely to occur during the first weeks of combination treatment and in patients with renal

impairment. Dosage adjustment of the antidiabetic medicine may be required with the concomitant use of a thiazide diuretic.

Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH) or stimulant laxatives

The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by drugs associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, salicylic acid derivatives).

Concomitant use of steroids or adrenocorticotropic hormone (ACTH) and thiazide diuretic may intensify electrolyte depletion and hypokalaemia.

Pressor amines (e.g. adrenalin)

Thiazide diuretics may decrease response to pressor amines. This decrease in response is not sufficient to preclude the use of pressor amines.

Calcium salts

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or Vitamin D must be prescribed, serum calcium levels should be monitored, and the dose adjusted accordingly.

Cardiac glycosides

Hypokalemia can sensitise or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).

Colestyramine and colestipol

The absorption of hydrochlorothiazide is reduced by colestipol or cholestyramine. Therefore, sulphonamide diuretics should be taken at least 1 hour before or 4-6 hours after intake of these agents.

Trimethoprim

Concomitant administration of ACE inhibitors and thiazides with trimethoprim increases the risk of hyperkalaemia.

Sotalol

Thiazide induced hypokalaemia can increase the risk of sotalol induced arrhythmia.

Allopurinol

Concomitant administration of ACE inhibitors and allopurinol increases the risk of renal damage and can lead to an increased risk of leucopoenia.

Ciclosporin
Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Lovastatin
Concomitant administration of ACE inhibitors and lovastatin increases the risk of hyperkalaemia.

Cytostatics, immunosuppressives, procainamide
Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects (see section 4.4).

Co-trimoxazole (trimethoprim/sulfamethoxazole)
Patients taking concomitant co-trimoxazole (trimethoprim/ sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).
Thiazides may increase the risk of adverse effects caused by amantadine.

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of ADCO ZETOMAX CO is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take ADCO ZETOMAX CO during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ADCO ZETOMAX CO should be stopped immediately and if appropriate, alternative therapy should be started.
Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spins bifida) and of kidney malformations. ADCO ZETOMAX CO passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms.
Oligohydramnios as well as hypotension, oliguria and anuria in new-borns, have been reported after administration of ADCO ZETOMAX CO during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

There is no experience with the removal of hydrochlorothiazide, which also crosses the placenta, from the neonatal circulation.
The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard. Diuretics do not prevent development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxaemia. Thiazides cross the placental barrier and appear in cord blood. Hazards include foetal or neonatal jaundice, thrombocytopenia and possible other adverse reactions which occur in the adult.

Breastfeeding
It is not known whether lisinopril is distributed into human breast milk; however, the thiazides do appear in human milk. If the medicine is deemed essential, the patient should stop nursing.

Fertility
No information available.

4.7 Effects on ability to drive and use machines
Patients taking ADCO ZETOMAX CO should exercise caution when driving or using machines as it might cause dizziness, fatigue, light-headedness and transient blurred vision.

4.8 Undesirable effects
a) Summary of safety profile
The most frequent adverse reactions include headache, dry mouth, dry cough, muscle cramps, dizziness, syncope, orthostatic effects (including orthostatic hypotension), diarrhoea, vomiting and renal dysfunction.

b) Tabulated summary of adverse reactions
The following side effects are listed according to the organ class system for ADCO ZETOMAX CO, as well as the individual components, lisinopril and hydrochlorothiazide:

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
ADCO ZETOMAX CO:		
Immune system disorders	Less frequent	Angioedema of the face, extremities, lips, tongue, glottis and/or larynx (see section 4.4).
Metabolism and nutrition disorders	Less frequent	Gout
	Frequent	Headache, dry mouth.

Nervous system disorders	Less frequent	Paraesthesia, dizziness and fatigue, which generally diminished when the dosages are reduced. Asthenia.
Cardiac disorders	Less frequent	Palpitation, chest discomfort.
Vascular disorders	Less frequent	Hypotension including orthostatic hypotension.
Respiratory, thoracic and mediastinal disorders	Frequent	Dry cough.
Gastrointestinal disorders	Less frequent	Diarrhoea, nausea, vomiting.
Skin and subcutaneous tissue disorders	Less frequent	Rash and photosensitivity.
Musculoskeletal, connective tissue and bone disorders	Frequent	Muscle cramps.
Reproductive system and breast disorders	Less frequent	Impotence.
Lisinopril		
Blood and lymphatic system disorders	Less frequent	Decreases in haemoglobin, decreases in haematocrit, bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease.
Immune system disorders	Frequency unknown	Anaphylactic/anaphylactoid reaction.
Endocrine disorders	Less frequent	Syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Metabolism and nutrition disorders	Less frequent	Hypoglycaemia.
Psychiatric disorders	Less frequent	Mood alterations, depressive symptoms. Mental confusion.
	Frequency unknown	Hallucinations.
	Frequent	Dizziness, headache, syncope.

Nervous system disorders	Less frequent	Paraesthesia, vertigo, taste disturbance, sleep disturbances. Olfactory disturbance.
Cardiac disorders	Less frequent	Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia.
Vascular disorders	Frequent	Orthostatic effects (including orthostatic hypotension).
	Less frequent	Raynaud's syndrome.
	Frequency unknown	Flushing.
Respiratory, thoracic and mediastinal disorders	Frequent	Cough (see section 4.4).
	Less frequent	Rhinitis. Bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia.
Gastrointestinal disorders	Frequent	Diarrhoea, vomiting.
	Less frequent	Nausea, abdominal pain and indigestion, dry mouth, pancreatitis, intestinal angioedema.
Hepatobiliary disorders	Less frequent	Elevated liver enzymes and bilirubin. Hepatitis - either hepatocellular or cholestatic, jaundice and hepatic failure (see section 4.4).*
Skin and subcutaneous tissue disorders	Less frequent	Rash, pruritus, hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4), urticaria, alopecia, psoriasis. Diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, cutaneous pseudolymphoma.**
Renal and urinary disorders	Frequent	Renal dysfunction.
	Less frequent	Uraemia, acute renal failure, oliguria/anuria.
Reproductive system and breast disorders	Less frequent	Impotence, gynaecomastia.
General disorders and administration site conditions	Less frequent	Asthenia, fatigue (which generally diminished when the dosages are reduced).

Investigations	Less frequent	Increases in blood urea, increases in serum creatinine, hyperkalaemia, hyponatraemia.
Hydrochlorothiazide		
Infections and infestations	Frequency unknown	Sialadenitis.
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Frequency unknown	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).
Blood and lymphatic system disorders	Frequency unknown	Leukopenia, neutropenia/ agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression.
Metabolism and nutrition disorders	Frequency unknown	Anorexia, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia, hypokalaemia, hypochloremic alkalosis and hypomagnesaemia), increases in cholesterol and triglycerides, gout.
Psychiatric disorders	Frequency unknown	Restlessness, depression, sleep disturbance.
Nervous system disorders	Frequency unknown	Loss of appetite, paraesthesia, light-headedness.
Eye disorders	Frequency unknown	Xanthopsia, transient blurred vision, acute myopia and acute angle-closure glaucoma.
Ear and labyrinth disorders	Frequency unknown	Vertigo.
Cardiac disorders	Frequency unknown	Postural hypotension.
Vascular disorders	Frequency unknown	Necrotising angiitis (vasculitis, cutaneous vasculitis).
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Respiratory distress (including pneumonitis and pulmonary oedema).
Gastrointestinal disorders	Frequency unknown	Gastric irritation, diarrhoea, constipation, pancreatitis.

Hepatobiliary disorders	Frequency unknown	Jaundice (intrahepatic cholestatic jaundice), glycosuria.
Skin and subcutaneous tissue disorders	Frequency unknown	Photosensitivity reactions, rash, systemic lupus erythematosus, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis.
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Muscle spasm, muscle weakness.
Renal and urinary disorders	Frequency unknown	Renal dysfunction, interstitial nephritis.
General disorders	Frequency unknown	Fever, weakness.

* Very rarely, it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving lisinopril/hydrochlorothiazide combination who develop jaundice or marked elevations of hepatic enzymes should discontinue lisinopril/hydrochlorothiazide combination and receive appropriate medical follow up.

** A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

c) Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

Limited data are available for overdose in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.
Additional symptoms of hydrochlorothiazide overdose are increased diuresis, depression of consciousness (incl. coma), convulsions, paresis, cardiac arrhythmias and renal failure.
If digitalis has also been administered hypokalaemia may accentuate cardiac arrhythmias.

Management

Treatment is symptomatic and supportive. The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the supine position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating lisinopril (e.g. emesis, administration of absorbents and sodium sulphate).
Therapy with ADCO ZETOMAX CO should be discontinued and the patient should be kept under very close supervision.
Lisinopril may be removed from the general circulation by haemodialysis (see section 4.4).
Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.
Bradycardia or extensive vagal reactions should be treated by administering atropine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1.3 Other hypotensives.
Pharmacotherapeutic group: Lisinopril and diuretics.
ATC code: C09BA03
Lisinopril/hydrochlorothiazide is a combination of an angiotensin converting enzyme inhibitor, lisinopril and a diuretic, hydrochlorothiazide. Both these components have been widely used alone and in combination for the treatment of hypertension due to additive effects.
Lisinopril is a peptidyl dipeptidase inhibitor and inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to angiotensin II. Angiotensin II is a vasoconstrictor peptide that also stimulates aldosterone secretion by the adrenal cortex.
Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion. Reduced aldosterone secretion may result in an increase in serum potassium concentration.
The mechanism of action through which lisinopril lowers blood pressure is mainly via suppression of the renin-angiotensin-aldosterone system; however, lisinopril also has antihypertensive effects in patients with low-renin hypertension.

ACE is identical to kininase II, an enzyme that degrades bradykinin. It could be possible that increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril. However, this remains to be elucidated.
Hydrochlorothiazide is a thiazide diuretic and an antihypertensive agent. It affects the distal renal tubular mechanism of electrolyte re-absorption and increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. The mechanism of the antihypertensive effects of the thiazides is unknown. Thiazides do not usually affect normal blood pressure.

5.2 Pharmacokinetic properties

The concomitant administration of lisinopril and hydrochlorothiazide has no clinical significant effect on the pharmacokinetics of either drug.
Lisinopril:
Approximately 60 % of lisinopril is absorbed after oral administration. The absorption varies between individuals (6 to 60 %).
Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours. Lisinopril has an effective half-life of 12 hours. Lisinopril does not bind to other serum proteins. The absorption of lisinopril is not affected by the presence of food in the gastrointestinal tract. Lisinopril does not undergo metabolism and absorbed drug is excreted unchanged entirely in the urine. Impaired renal function decreases elimination of lisinopril. This decrease only becomes clinically important when the glomerular filtration rate is below 30 ml/ min. Lisinopril can be removed by dialysis.
Older patients have higher blood levels and higher values for the area under the plasma concentration time curve than younger patients.
Hydrochlorothiazide:
The plasma half-life of hydrochlorothiazide can vary between 5 and 15 hours.
Approximately 60 % of the dose is eliminated unchanged within 24 hours. After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts 6 to 12 hours.

5.3 Preclinical safety data

No information available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ADCO ZETOMAX CO 10/12,5:
Calcium hydrogen phosphate dihydrate
Croscarmellose sodium

Iron oxide red (E172 / C177492)
Iron oxide yellow (E172 / C177492)
Magnesium stearate
Mannitol
Pregelatinised maize starch
Pigment blend PB-27222 Beige

ADCO ZETOMAX CO 20/12,5:
Calcium hydrogen phosphate dihydrate
Croscarmellose sodium
Magnesium stearate
Mannitol
Pregelatinised maize starch.

ADCO ZETOMAX CO 20/25:
Calcium hydrogen phosphate dihydrate
Croscarmellose sodium
Iron oxide red (E172)
Iron oxide yellow (E172)
Magnesium stearate
Mannitol
Pregelatinised maize starch.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store at or below 25 °C.
Store tablets in a cool, dry place.
Store in the original packaging.
Do not remove the blister from the carton until required for use.

6.5 Nature and contents of container
Blister strips of clear transparent PVC/PVDC film and aluminium foil, packed into cardboard boxes of 30 tablets each or 50 ml, white, cylindrical polypropylene plastic container and a white

circular, low density, polyethylene plastic cap (with a seal with a small tab to open it), each containing a silica gel dessicant and 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBERS

ADCO ZETOMAX CO 10/12,5: 37/7.1.3/0160
ADCO ZETOMAX CO 20/12,5: 37/7.1.3/0162
ADCO ZETOMAX CO 20/25: 37/7.1.3/0161

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 June 2005

10. DATE OF REVISION OF THE TEXT

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