SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

ADCO ZETOMAX 5 mg tablet
ADCO ZETOMAX 10 mg tablet
ADCO ZETOMAX 20 mg tablet

COMPOSITION

ADCO ZETOMAX 5 mg

Each tablet contains lisinopril 5 mg (as the dihydrate salt).
List of excipients: Calcium hydrogen phosphate dihydrate, croscarmellose sodium, magnesium stearate, mannitol, pregelatinised maize starch.
Sugar free.

ADCO ZETOMAX 10 mg

Each tablet contains lisinopril 10 mg (as the dihydrate salt).
List of excipients: Calcium hydrogen phosphate dihydrate, croscarmellose sodium, magnesium stearate, mannitol, pregelatinised maize starch, pigment blend PB-24823 pink (composed of iron oxide red (E 172), iron oxide black (E 172), iron oxide yellow (E 172).
Sugar free.

ADCO ZETOMAX 20 mg

Each tablet contains lisinopril 20 mg (as the dihydrate salt)
List of excipients: Calcium hydrogen phosphate dihydrate, croscarmellose sodium, magnesium stearate, mannitol, pregelatinised maize starch and pigment blend PB-24824 pink (composed of iron oxide red (E 172), iron oxide black (E 172), iron oxide yellow (E 172).
Sugar free.

CATEGORY AND CLASS PHARMACOLOGICAL ACTION

A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor.
ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor angiotensin II which is involved in vascular control and function through many different mechanisms, including stimulation of aldosterone secretion by the adrenal cortex.
The primary mode of action of lisinopril is to inhibit ACE, thereby decreasing vasopressor activity and aldosterone secretion.

Decreased angiotensin II concentrations result in a secondary increase in plasma renin activity (PRA), through removal of the negative feedback on renin secretion, and a direct reduction in aldosterone secretion.
Lisinopril has antihypertensive activity in the presence of low to normal plasma renin concentrations.

Lisinopril reduces peripheral arterial resistance.
Other possible mechanisms contributing to the activity of ACE-inhibitors include bradykinin-induced vasodilation, release of prostaglandins, attenuation of sympathetic nervous system activity, and inhibition of tissue enzyme-converting activity. ACE, also known as kininase II, is the enzyme that degrades bradykinin, a potent vasodepressor peptide.

Pharmacokinetic properties
Following oral administration, the onset of action of lisinopril is approximately one hour, with peak serum lisinopril concentrations which are observed within seven hours.
The absorption of lisinopril is not influenced by food, absorption is approximately 25 % with wide variability of 6-60 % between patients.
Lisinopril is not metabolised and is eliminated primarily by renal excretion in the unchanged form with a terminal half-life of approximately 12 hours.
Lisinopril is removed by hemodialysis.
Lisinopril is not significantly bound to plasma protein.
Elderly patients exhibit higher blood levels and higher values for the area under the plasma concentration-time curve than younger patients.
The excretion of lisinopril in patients with renal insufficiency is decreased when creatinine clearance is less than 30 ml per minute.

INDICATIONS
ADCO ZETOMAX is indicated for:
Mild to moderate hypertension
The treatment of mild to moderate hypertension as monotherapy or in combination with a thiazide diuretic.

Congestive heart failure
The management of congestive heart failure in combination with diuretics and digitalis therapy, in patients not responding to other measures.

Prevention of left ventricular dysfunction following myocardial infarction
The treatment of patients that is hemodynamically stable, within 24 hours after acute myocardial infarction, to prevent the subsequent development of left ventricular dysfunction or heart failure and to improve survival. Patients should also receive as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers.

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardico

(GISSI-3) study was a multicentre randomised clinical trial performed on 19 394 patients. The GISSI-3 study assessed the efficacy of lisinopril as monotherapy and in combination with glyceryl trinitrate in improving survival and ventricular function after acute myocardial infarction.

The study examined the effects of short term (6 week) treatment with lisinopril, nitrates, their combination, or no therapy, on short term and longer term mortality, and on markedly impaired cardiac function. All patients continued to receive routine therapies, including thrombolytics (72 %), aspirin (84 %) and beta-blockers (31 %).
The protocol excluded patients with hypotension (systolic blood pressure ≤ 100 mmHg), severe heart failure, cardiogenic shock and renal dysfunction (serum creatinine > 177 µmol/L and/or proteinuria > 500 mg/24h).

Although patients randomised to receive lisinopril for up to six weeks fared numerically better on the combined end-point at 6 months, the open nature of the assessment of heart failure along with substantial loss to follow-up echocardiography and substantial excess use of lisinopril between 6 weeks and 6 months in the group randomised to 6 weeks of lisinopril, precluded any conclusion about this endpoint.
Furthermore, in the predefined high risk groups of elderly and female patients, the favourable effects of lisinopril alone or with concurrent glyceryl trinitrate were demonstrated for the combined endpoint.
The primary outcomes of the study were all-cause mortality and a combined end-point – the number of patients who died and who had late (day 4) clinical congestive heart failure or had extensive left ventricular damage (defined as ejection fraction of 35 % or less or an akinetic-dyskinetic [A-D] score > 45 %).

Patients receiving lisinopril (n=9 646) alone or with nitrates, were found to have an 11 % lower relative risk of death (2p [two-tailed] = 0, 04) compared to patients receiving no lisinopril (n = 9 672) (619 patients [6,4 %] vs 693 patients [7,2 %] respectively, representing a 0,8 % absolute reduction in death) at six weeks. This reduction in mortality at six months was not significant and was not a primary outcome measure.

CONTRAINDICATIONS

- Hypersensitivity to this product or any other ACE-inhibitor, particularly patients with a history of angioedema associated with previous ACE-inhibitor therapy.
- Hereditary or idiopathic angioneurotic oedema.
- Patients with aortic stenosis or outflow tract obstruction.
- 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 **WARNINGS AND SPECIAL PRECAUTIONS**).
- Concomitant use with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1,73 m^2) (See **INTERACTIONS**).
- **ADCO ZETOMAX** is contraindicated throughout pregnancy. See **'WARNINGS and SPECIAL PRECAUTIONS'** and **'HUMAN REPRODUCTION'**.

WARNINGS and SPECIAL PRECAUTIONS

Pregnancy

Should a woman become pregnant while receiving an ACE-inhibitor, the treatment must be stopped promptly and switched to a different category of medicine.
Should a woman receiving an ACE-inhibitor, contemplate pregnancy, the doctor must institute alternative medication.

ACE-inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the second and third trimesters. Treatment should be discontinued immediately, preferably in the first trimester.

Oligohydramnios which may result in limb contractures, craniofacial deformities and hypoplastic lung development, has also been reported.

ACE-inhibitors pass through the placenta and can be presumed to cause disturbances in foetal blood pressure regulatory mechanisms. Hypotension, renal failure, hyperkalaemia, oliguria and anuria in newborns have been reported after administration of ACE-inhibitors in the second and third trimester. Cases of defective skull ossification have been observed.
Prematurity and low birth mass can occur.

Infants exposed *in utero* to ACE-inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia. The adverse effects to the embryo and foetus do not appear to have resulted from intra-uterine exposure limited to the first trimester. Lisinopril has been removed from the neonatal circulation by peritoneal dialysis.

In patients with coronary insufficiency, ischemia may be aggravated as a result of reduced blood pressure; cerebrovascular accident or myocardial infarction could be precipitated.

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 **CONTRAINDICATIONS**). 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.

Hypersensitivity / Angioedema:

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx may occur. This may occur at any time during therapy, especially following the first dose of **ADCO ZETOMAX**. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, difficulty in breathing) and to discontinue medication immediately until they have consulted with their physician.

The patient should be treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Angioedema associated with laryngeal oedema or tongue oedema may be fatal. Where there is involvement of the tongue, glottis, or larynx which is likely to cause airway obstruction, especially in patients with a history of airway surgery, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Black patients receiving ACE-inhibitor therapy have been reported to have a higher incidence of angioedema compared to non-black patients.

Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema while receiving an ACE-inhibitor.
Patients being treated concomitantly with mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (see **INTERACTIONS**).

Anaphylactoid reactions in haemodialysis patients
Clinical evidence has shown that patients haemodialyzed using certain high-flux membranes (such as polyacrylonitrile membranes) are likely to experience anaphylactoid reactions with concomitant ACE-inhibitor treatment. This combination should be avoided, either by use of alternative antihypertensive medicines, or alternative membranes for haemodialysis.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis
There has been reports of patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulphate experiencing life-threatening anaphylactoid reactions. These reactions can be avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactoid reactions during desensitization
Patients receiving ACE-inhibitors during desensitizing treatment with, for example hymenoptera venom, have sustained life-threatening anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE-inhibitors were temporarily withheld, but they have reappeared upon inadvertent re-administration.

Hepatic failure
There has been reports that ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant necrosis and can sometimes be fatal. The mechanism of this syndrome is not understood. Patients being treated with **ADCO ZETOMAX**, who develop jaundice or marked elevations of hepatic enzymes, should receive appropriate medical follow-up and treatment with **ADCO ZETOMAX** should be discontinued.

Symptomatic hypotension

Patients should be cautioned to report light headedness, especially during the first few days of **ADCO ZETOMAX** therapy. If actual syncope occurs, the patients should be told to discontinue medication until they have consulted with their physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as a severe dietary sodium restriction, dialysis, previous diuretic therapy, vomiting or diarrhoea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

Sudden reduction by the initial dose of ACE-inhibitor in the angiotensin II levels that have been maintaining patients at a near-normotensive state, or who have low blood pressure may also result in sudden and severe hypotension. This effect should be anticipated and is not a reason to discontinue treatment.

However, should hypotension become symptomatic, dosage reduction or discontinuation of **ADCO ZETOMAX** may be necessary.

Symptomatic hypotension may occur in uncomplicated hypertensive patients and has been observed in patients with congestive heart failure, with or without renal insufficiency. It is most likely to occur in patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatremia or functional renal impairment.

In these patients, initiation of therapy and dosage adjustment should be monitored under close medical supervision.

Similar considerations should apply to patients with ischemic heart or cerebrovascular disease in whom excessive fall 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, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses; however, lower doses of lisinopril or any concomitant diuretic therapy should be considered if this event occurs.

Hypotension in acute myocardial infarction

Treatment with **ADCO ZETOMAX** must not be initiated in acute myocardial infarction patients who are at risk of further serious hemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100 mm Hg or lower or with cardiogenic shock.

During the first 3 days following the infarction, if the systolic blood pressure is 120 mm Hg or lower, the dose should be reduced. Maintenance doses should be reduced to 5 mg or temporarily to 2,5 mg if systolic blood pressure is 100 mm Hg or lower. If hypotension persists (systolic blood pressure less than 90 mm Hg, for more than 1 hour) **ADCO ZETOMAX** should be withdrawn.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

ADCO ZETOMAX should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Surgery/anaesthesia
Caution should be exercised when patients undergo anaesthesia since ACE-inhibitors have been shown to block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion.

Neutropenia/agranulocytosis
ACE-inhibitors have been associated with agranulocytosis and bone marrow depression in patients with uncomplicated hypertension and in patients with auto-immune disease, especially systemic lupus erythematosus or scleroderma.
ADCO ZETOMAX must be used with extreme caution in patients with collagen vascular disease, patients who are on immunosuppressant therapy, and /or on treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Neutropenia has rarely occurred in patients with normal renal function and no other complications.

Agranulocytosis has been rarely reported during treatment with **ADCO ZETOMAX**. Monitoring of white blood cell counts especially in patients with collagen vascular disease and/or renal disease is advised. Patients should be told to promptly report any indication of infection (e.g. sore throat, fever) which does not resolve within two days.
Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor.

Impaired renal function
In patients with impaired renal function (creatinine clearance
< 80 ml/min), the initial dosage should be adjusted according to the patients' creatinine clearance and then according to the patient's response to the treatment (see **DOSAGE AND DIRECTIONS FOR USE**).
In patients with congestive heart failure, hypotension following the initiation of therapy with ACE-inhibitors may lead to some further impairment in renal function. Acute renal failure has been reported in this situation.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE-inhibitors, increases in blood urea and serum creatinine, reversible upon discontinuation of therapy, have been seen. Such findings are especially likely to occur in patients with renal insufficiency. In some hypertensive patients with no apparent pre-existing renal vascular disease, increases in blood urea and serum creatinine have occurred, especially when **ADCO ZETOMAX** has been given together with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of **ADCO ZETOMAX** and/or discontinuation of the diuretic and/or **ADCO ZETOMAX** may be required.
In acute myocardial infarction, treatment with **ADCO ZETOMAX** should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentration exceeding 177 μmol/L and/or proteinurea exceeding 500 mg/24 hours). If renal dysfunction develops during treatment with **ADCO ZETOMAX** (serum creatinine concentration exceeding 265 μmol/L or a doubling of the pre-treatment value) then withdrawal of **ADCO ZETOMAX** should seriously be considered.

Diabetic patients
ACE-inhibitors have been associated with hypoglycaemia in diabetic patients on insulin or oral hypoglycaemic agents; closer monitoring of diabetic patients may be required.

Hyperkalaemia and potassium sparing diuretics
Patients on **ADCO ZETOMAX** alone may have increased serum potassium levels. This effect may help to reduce the hypokalaemia induced by thiazide diuretics.
Caution should be exercised in diabetic patients and patients with impaired renal function due to the risk for the development of hyperkalaemia.
Patients at risk of developing 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 and co-trimoxazole).
Because of the risk of further potentiating increases in serum potassium with potassium sparing diuretics, it is advised that if such combination therapy is indicated, it be initiated with caution and the patient's serum potassium levels be closely monitored. Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
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). Concomitant use is not recommended (see **INTERACTIONS**).
Dual blockade therapy should only be done under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure and only if it is considered absolutely necessary.
ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Race
ACE inhibitors cause a higher rate of angioedema in black patients than in other race groups.
ACE inhibitors may be less effective in lowering blood pressure in black patients than in other race groups, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough
Has been reported with ACE-inhibitor use. The cough is characteristically non-productive, persistent and resolves after ACE-inhibitor withdrawal.
ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Effects on ability to drive and use machines
Dizziness and tiredness may occur during treatment with **ADCO ZETOMAX.**

INTERACTIONS

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 **CONTRAINDICATIONS**).

Antihypertensive medicines

Additive falls in blood pressure may occur when **ADCO ZETOMAX** is combined with other antihypertensive medicines such as glyceryl trinitrate and other nitrates or other vasodilators. 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 (including acute renal failure) compared to the use of a single RAAS-acting agent (see **CONTRAINDICATIONS** and **WARNINGS and SPECIAL PRECAUTIONS**). Antihypertensive medicines such as beta-blocking agents may increase the hypotensive effect of ACE-inhibitors.

Medicines 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 (see **WARNINGS and SPECIAL PRECAUTIONS**).

Diuretics

The antihypertensive effect is usually intensified when a diuretic is added to the therapy of a patient being treated with **ADCO ZETOMAX**.

Patients already on diuretics, especially those on recently instituted diuretic therapy, may experience an excessive reduction of blood pressure after initiation of therapy with **ADCO ZETOMAX**. Hypotensive effects after the first dose of lisinopril may be minimized by discontinuing the diuretic a few days prior to initiation of therapy.

Potassium sparing diuretics, potassium containing medicines and potassium supplements and other medicines that may increase serum potassium levels

Concurrent administration may cause hyperkalaemia (see **WARNINGS and SPECIAL PRECAUTIONS**).

The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes and other medicines that may increase serum potassium levels, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium. Appropriate monitoring of potassium must be undertaken. (see **WARNINGS and SPECIAL PRECAUTIONS**).

If a potassium-losing diuretic is given with **ADCO ZETOMAX**, diuretic-induced hypokalaemia may be improved.

Co-trimoxazole (trimethoprim/sulfamethoxazole): Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may have an increased risk for hyperkalaemia (see **WARNINGS and SPECIAL PRECAUTIONS**).

Cyclosporin: Hyperkalaemia may occur with concomitant use of ACE-inhibitors.
Bone marrow depressants: Concurrent administration with ACE-inhibitors may result in an increased risk of development of potentially fatal neutropenia/and or agranulocytosis.
Estrogens: Estrogen induced fluid retention may increase blood pressure; the patient should be carefully monitored to confirm that the desired effect with lisinopril is obtained.

Tricyclic antidepressants / Antipsychotics / anaesthetics
Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see **WARNINGS and SPECIAL PRECAUTIONS**).
ACE-inhibitors may enhance the hypotensive effects of certain anaesthetic medicines.
Alcohol may enhance the hypotensive effect of **ADCO ZETOMAX**.
Postural hypotension may occur with the concomitant use of ACE-inhibitors and narcoleptic medicines and antipsychotics.

Lithium
Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE-inhibitor therapy due to the sodium losing effect of these agents. These medicines should be administered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Non-steroidal anti-inflammatory drugs (NSAIDs), especially indomethacin and including acetylsalicylic acid ≥ 3 g/day
Concurrent use of these agents (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effects of ACE-inhibitors.

Concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, which may include acute renal failure and an increase in serum potassium, especially in patients with impaired pre-existing renal function. These effects are usually reversible. The combination should be administered with caution, especially in the elderly. Patients should remain adequately hydrated and monitoring renal function after initiation of concomitant therapy, and periodically thereafter should be considered.

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

Sympathomimetics
Concurrent use of these agents may reduce the antihypertensive effects of ACE-inhibitors. The patient should be carefully monitored to confirm that the desired effect is being obtained.

Antidiabetics
Concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood glucose-lowering effect with risk of hypoglycaemia. This effect appeared to be more likely to occur during the first weeks of concomitant treatment and in patients with renal impairment.

Allopurinol, cytostatic agents, and immunosuppressive agents
The concomitant administration of allopurinol, cytostatic agents or immunosuppressive agents, systemic corticosteroids or procainamide may lead to an increased risk of leukopenia.

HUMAN REPRODUCTION
ADCO ZETOMAX is contraindicated throughout pregnancy. See '**CONTRAINDICATIONS'** and **'WARNINGS and SPECIAL PRECAUTIONS'**.
It is not known whether **ADCO ZETOMAX** is secreted in human breast milk. Safety in lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE
ADCO ZETOMAX may be administered without regard to meals. **ADCO ZETOMAX** should be administered as a single daily dose and taken at approximately the same time each day.
Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE-inhibitor, it is preferable that the first dose be given at bedtime.
The hemodynamic effect is observed within 1 to 2 hours of a single oral dose and the maximum effect occurs after about 6 hours, although the full effect may not develop for several weeks during chronic dosing. The hemodynamic action lasts for about 24 hours following once daily dosing.
Mild to moderate hypertension
Monotherapy:
The recommended initial dosage of **ADCO ZETOMAX** in patients not on diuretics is 10 mg once daily.
Depending upon clinical response, patient's dosage may be titrated (by doubling the dose) to a maintenance dosage of 10 to 20 mg/day given as a single dose. The maximum dose is 40 mg per day.

Concomitant diuretics:
Previous diuretic therapy should be withdrawn 2-3 days before initiating lisinopril therapy.
In patients who are also being treated with a diuretic, the initial dosage of **ADCO ZETOMAX** is 2,5 mg - 5 mg in order to determine if excess hypotension will occur. When therapy is initiated, such patients should be placed under careful medical supervision for at least 2 hours and until blood pressure has stabilised for at least an additional hour. The dosage should subsequently be titrated (as described above) to the optimal response (see **WARNINGS and SPECIAL PRECAUTIONS**).

Dosage in patients with renal impairment:
In patients with renal impairment, in whom diuretic therapy cannot be discontinued or in patients who are sodium- and water-depleted for any reason, the lower dose (5 mg) should be used as initial dose. An initial dose of 2,5 mg should be used in patients with a creatinine clearance less than 10 ml per minute.
Provided renal function does not deteriorate, dosage adjustment should be based on clinical response.

Renovascular hypertension:
Caution should be exercised in these patients due to the possibility of exaggerated response. The initial dose should be 2,5 mg or 5 mg and the patient monitored carefully.

Congestive heart failure
The recommended initial dosage in patients with congestive heart failure is a single dose of 2,5 mg to 5 mg, following which the patient should be monitored closely for symptomatic hypotension. Patients may be titrated up to a maintenance dose of 5 mg to 20 mg daily given in two doses with concomitant diuretic and/or cardiac glycoside therapy. Patients can, however, normally be maintained effectively on doses of 10 to 20 mg per day given in one or two doses with concomitant therapy.
In patients with heart failure taking loop diuretics, severe first dose hypotension is common, but temporary withdrawal of the diuretic may cause rebound oedema. Thus, treatment should be initiated with a low dose under close medical supervision.

Myocardial infarction
Following myocardial infarction, treatment should be started within 24 hours of the onset of symptoms in an initial dose of 5 mg once daily for two days, then increased to 10 mg once daily. An initial dose of 2,5 mg once daily is recommended for patients with a low systolic blood pressure.
If hypotension occurs (systolic blood pressure less than or equal to 100 mmHg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2, 5 mg if necessary. Should prolonged hypotension occur (systolic blood pressure less than 90 mmHg for more than 1 hour) treatment should be withdrawn.
Dosing should continue for 6 weeks. The benefits appear to be greatest in patients with large myocardial infractions and with evidence of impaired left ventricular function. Patients who develop symptoms of heart failure should continue with treatment (see **DOSAGE AND DIRECTIONS FOR USE: Congestive heart failure**). **ADCO ZETOMAX** is compatible with intravenous or transdermal glyceryl trinitrate.

Elderly
Some patients may be more sensitive to the hypotensive effect of ACE-inhibitors and thus caution is advised when treatment is initiated.
When advanced age is associated with a decrease in renal function, dosage adjustment as depicted under '*Dosage in patients with renal impairment'* should be followed.

Paediatrics:
Safety and efficacy have not been established.

SIDE EFFECTS

Gastrointestinal disorders	
Frequent:	Diarrhoea and vomiting.
Less frequent:	Dry mouth or throat, dyspepsia, nausea abdominal pain, constipation, pancreatitis, intestinal angioedema, hepatitis - hepatocellular or cholestatic, jaundice and hepatic failure (see **WARNINGS and SPECIAL PRECAUTIONS**).
Frequency unknown:	Stomatitis, taste disturbances.

Metabolism and nutrition disorders	
Less frequent:	Hypoglycaemia.

Nervous system and psychiatric disorders	
Frequent:	Headache, dizziness.
Less frequent:	Vertigo, paraesthesia, mood and sleep disturbances, blurred vision, mental confusion, fatigue, taste disturbance, hallucinations, olfactory disturbance.
Frequency unknown:	Depression, syncope, nervousness.

Cardiac and vascular disorders	
Frequent:	Orthostatic effects (including hypotension).
Less frequent:	Palpitations, tachycardia, Raynaud's phenomenon, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see **WARNINGS AND SPECIAL PRECAUTIONS)**.
Frequency unknown:	Chest pain, vasodilatation.

Respiratory, thoracic and mediastinal disorders	
Frequent:	Cough (See **WARNINGS AND SPECIAL PRECAUTIONS**).
Less frequent:	rhinitis, sinusitis, bronchospasm, allergic alveolitis / eosinophilic pneumonia.
Frequency unknown	Upper respiratory tract infection.

Blood and the lymphatic system disorders	
Less frequent:	Leukopenia, neutropenia and agranulocytosis (especially in patients with renal failure and in those with collagen vascular disorders such

	as systemic lupus erythematosus and scleroderma), anaemia, thrombocytopenia, decreases in haemoglobin, decreases in haematocrit, bone marrow depression, haemolytic anaemia, lymphadenopathy, autoimmune disease.

Immune system disorders	
Frequency unknown:	Anaphylactic/anaphalactoid reaction.

Skin and subcutaneous tissue disorders	
Less frequent:	Pruritus, urticaria, diaphoresis, skin rashes (including erythema multiforme, Steven-Johnson syndrome and toxic epidermal necrolysis), exfoliative dermatitis, hypersensitivity reactions, alopecia, arthralgia, angioedema, psoriasis, pemphigus, sweating and cutaneous pseudolymphoma. Angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see **WARNINGS and SPECIAL PRECAUTIONS**).

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

Renal and urinary disorders	
Frequent:	Renal dysfunction.
Less frequent:	Oliguria/anuria, acute renal failure, uraemia.

Endocrine disorders	
Less frequent:	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Reproductive system and breast disorders	
Less frequent:	Impotence.
Less frequent:	Gynaecomastia.

General disorders and administration site conditions	
Less frequent:	Fatigue, asthenia.

Musculoskeletal, connective tissue and bone disorders	
Frequency unknown:	Myalgia, muscle cramps.

Investigations

Less frequent:	hyperkalaemia, hyponatremia, increases in blood urea, increases in serum creatinine, increases in liver enzymes, increases in serum bilirubin.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
Symptoms of overdosage are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure. Lisinopril may be removed from the general circulation by haemodialysis.
Refer to **'SIDE EFFECTS AND SPECIAL PRECAUTIONS'**.
Treatment is symptomatic and supportive.

IDENTIFICATION
ADCO ZETOMAX 5 mg: White, round, flat tablets scored on both sides.
ADCO ZETOMAX 10 mg: Light pink, round, biconvex tablets scored on one side.
ADCO ZETOMAX 20 mg: Pink, round, biconvex tablets scored on one side.

PRESENTATION
Blister packs of 30 tablets.

STORAGE INSTRUCTIONS
Store at or below 25 ºC.
Store in a cool, dry place.
Store in the original packaging.
Do not remove the blister from the carton until required for use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS
ADCO ZETOMAX 5 mg: 33/7.1.3/0513
ADCO ZETOMAX 10 mg: 33/7.1.3/0514
ADCO ZETOMAX 20 mg: 33/7.1.3/0515

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
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Namibia: Adco-Zetomax 5 mg tablet: 05/7.1.3/0273 **NS2**
Namibia: Adco-Zetomax 10 mg tablet: 05/7.1.3/0271 **NS2**
Namibia: Adco-Zetomax 20 mg tablet: 05/7.1.3/0272 **NS2**

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