

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zofenopril / Hydrochlorothiazide Mylan 30 mg / 12.5 mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 30 mg of zofenopril calcium (equivalent to 28.7 mg zofenopril) and 12.5 mg hydrochlorothiazide.

Excipient with known effect:

Each film-coated tablet contains 47.50 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Beige, film-coated, round, biconvex tablet debossed with “M” on one side of the tablet and “Z” over the score and “H” below the score on the other side of the tablet.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild to moderate essential hypertension.

This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on zofenopril alone.

4.2 Posology and method of administration

Posology

Zofenopril / Hydrochlorothiazide Mylan should be used once daily. Dose titration with the individual components (*i.e.* zofenopril and hydrochlorothiazide) is recommended before changing to the fixed dose combination.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered.

Adults (18 to 65 years of age)

Patients without volume or salt depletion

The usual effective dose is one tablet once daily.

Patients suspected of volume or salt depletion

The use of zofenopril / hydrochlorothiazide is not recommended.

Older people (over 65 years)

In older people with normal creatinine clearance no dose adjustment is necessary.

In older people with reduced creatinine clearance (less than 45 mL/min) the use of zofenopril / hydrochlorothiazide is not recommended.

Creatinine clearance may be estimated from serum creatinine by the following Cockcroft-Gault formula:

$$\text{CrCl (mL/min)} = \frac{[(140 - \text{age}) * \text{weight (Kg)}]}{72 * \text{serum Cr (mg/dL)}}$$

The above method provides creatinine clearance in males. For females the value obtained should be multiplied by 0.85.

Paediatric population (under 18 years)

The safety and efficacy of zofenopril / hydrochlorothiazide in children and adolescents has not been established. Therefore, its use is not recommended.

Patients with renal impairment and dialysis

In hypertensive patients with mild impairment (creatinine clearance > 45 mL/min) the same dose level and once-daily regimen of zofenopril / hydrochlorothiazide can be employed as for patients with normal renal function.

In patients with moderate to severe impairment (creatinine clearance < 45 mL/min) its use is not recommended (see section 4.4).

In patients with severe renal impairment (creatinine clearance < 30 mL/min) zofenopril / hydrochlorothiazide is contraindicated (see section 4.3).

In hypertensive patients maintained on dialysis the use of zofenopril / hydrochlorothiazide is not recommended.

Patients with hepatic impairment

In hypertensive patients with mild to moderate hepatic impairment, where the 30 mg dose of zofenopril alone has been achieved, the same dose regimen can be employed as for patients with normal hepatic function.

In hypertensive patients with severe liver impairment zofenopril / hydrochlorothiazide is contraindicated.

Method of administration

For oral use.

Zofenopril / Hydrochlorothiazide Mylan can be taken with or without food.

To ease swallowing, tablets may be broken in two parts and swallowed one half after the other, at the prescribed time of administration.

4.3 Contraindications

- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Hypersensitivity to the active substances, other ACE-inhibitors or sulfonamide-derived substances or to any of the excipients listed in section 6.1.
- History of angioneurotic oedema associated with previous ACE-inhibitor therapy.
- Hereditary/idiopathic angioneurotic oedema.
- Severe hepatic impairment.
- Severe renal impairment (creatinine clearance < 30 mL/min).
- Bilateral renal artery stenosis or unilateral renal artery stenosis in cases of a solitary single kidney.
- The concomitant use of zofenopril / hydrochlorothiazide with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

ZOFENOPRIL

Hypotension

As with other ACE-inhibitors and diuretics, zofenopril / hydrochlorothiazide may cause a profound fall in blood pressure especially after the first dose, although symptomatic hypotension is seen rarely in uncomplicated hypertensive patients.

It is more likely to occur in patients who have been volume and electrolyte depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8).

In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is more likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment.

In patients at increased risk of symptomatic hypotension, treatment should be started under close medical supervision preferably in the hospital, with low doses and careful dose titration. If possible, diuretic treatment should be discontinued temporarily when therapy with zofenopril / hydrochlorothiazide is initiated.

Such considerations apply also to patients with angina pectoris or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

If hypotension develops, the patient should be placed in a supine position. Volume repletion with intravenous normal saline may be required. The occurrence of hypotension after the initial dose does not preclude subsequent careful dose titration with each component of the medicinal product after effective management.

Patients with renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE-inhibitors. Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only mild changes in serum creatinine even in patients with unilateral renal artery stenosis.

In these patients, therapy should be initiated under close medical supervision with low dose, careful titration and monitoring of renal function.

Patients with renal insufficiency

Close monitoring of renal function during therapy should be performed as deemed appropriate. Renal failure has been reported in association with ACE-inhibitors, mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. Some patients, with no apparent pre-existing renal disease have developed increases in blood urea and creatinine concentrations, particularly when a diuretic is given concomitantly. Dosage reduction of the individual components may be required. It is recommended that the renal function be monitored closely during the first few weeks of therapy.

Patients who are dialysed

Patients who are dialysed using high-flux polyacrylonitrile membranes (*e.g.* AN 69) and treated with ACE-inhibitors are likely to experience anaphylactoid reactions such as facial swelling, flushing, hypotension and dyspnoea within a few minutes of commencing haemodialysis. It is recommended to use an alternative membrane or an alternative antihypertensive medicinal product.

The efficacy and safety of zofenopril in myocardial infarction patients undergoing haemodialysis has not been established. Therefore, it should not be used in these patients.

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 ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

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.

Patients on LDL apheresis

Patients treated with an ACE-inhibitor undergoing LDL apheresis with dextran sulfate may experience anaphylactoid reactions similar to those seen in patients undergoing haemodialysis with high-flux membranes (see above). It is recommended that an agent from another class of antihypertensive products is used in these patients.

Anaphylactic reactions during desensitisation or after insect bites

Rarely, patients receiving ACE-inhibitors during desensitisation treatment (e.g. hymenoptera venom) or after insect bites have experienced 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 of the medicinal product. Therefore, caution should be used in patients treated with ACE-inhibitors undergoing such desensitisation procedures.

Kidney transplantation

There is no experience regarding the administration of zofenopril / hydrochlorothiazide in patients with a recent kidney transplantation. Its use in transplant recipients is therefore not recommended.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive products acting through inhibition of the renin-angiotensin system. Therefore the use of zofenopril is not recommended.

Hypersensitivity/angioedema

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx may occur in patients treated with ACE-inhibitors which occurs most frequently during the first weeks of treatment. However in rare cases severe angioedema may develop after long-term treatment with an ACE-inhibitor. Treatment with ACE-inhibitors should promptly be discontinued and replaced by an agent belonging to another class of antihypertensive products.

Angioedema involving the tongue, glottis or larynx may be fatal. Emergency therapy should be given including, but not necessarily limited to, immediate subcutaneous adrenaline solution 1:1,000 (0.3 to 0.5 ml) or slow intravenous adrenaline 1 mg/ml (which should be diluted as instructed) with close monitoring of ECG and blood pressure. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

Even in such instances where swelling of only the tongue is involved, without respiratory distress, patients may require observation since treatment with antihistamines and corticosteroids may not be sufficient.

ACE-inhibitors cause a higher rate of angioedema in black patients than in 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 (see section 4.3).

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)

Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

Cough

During treatment with ACE-inhibitors a dry and non-productive cough may occur which disappears after discontinuation of therapy. ACE-inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Hepatic failure

Rarely, ACE-inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE-inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE-inhibitor and receive appropriate medical follow-up.

Hyperkalaemia

Hyperkalaemia may occur during treatment with an ACE-inhibitor. This effect is usually attenuated by the potassium depleting effect of thiazide diuretics. 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 in patients taking other active substances associated with increases in serum potassium (*e.g.* heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole). If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Surgery/anaesthesia

ACE-inhibitors may cause hypotension or even hypotensive shock in patients undergoing major surgery or during anaesthesia, since they may block angiotensin II formation secondary to compensatory renin release. If it is not possible to withhold the ACE-inhibitor, intravascular and plasma volumes should be carefully monitored.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy

ACE-inhibitors should be used with caution in patients with mitral valve stenosis and left ventricular outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Neutropenia/agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE-inhibitors. The risk of neutropenia appears to be dose- and type-related and is dependent on patient's clinical status. It is rarely seen in uncomplicated patients but may occur in patients with some degree of renal impairment especially when it is associated with collagen vascular disease *e.g.* systemic lupus erythematosus, scleroderma and therapy with immunosuppressive agents, treatment with allopurinol or procainamide, or a combination of these complicating factors. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy.

If zofenopril is used in such patients, it is advised that white blood cell count and differential counts should be performed prior to therapy, every 2 weeks during the first 3 months of zofenopril therapy, and periodically thereafter. During treatment all patients should be instructed to report any sign of infection (*e.g.* sore throat, fever) when a differential white blood cell count should be performed. Zofenopril and other concomitant medication (see section 4.5) should be withdrawn if neutropenia (neutrophils less than $1,000/\text{mm}^3$) is detected or suspected. It is reversible after discontinuation of the ACE-inhibitor.

Psoriasis

ACE-inhibitors should be used with caution in patients with psoriasis.

Proteinuria

Proteinuria may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE-inhibitors. Patients with prior renal disease should have urinary protein estimation (dip-stick on first morning urine) prior to treatment, and periodically thereafter.

Diabetic patients

The glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic products or insulin, during the first month of treatment with an ACE-inhibitor (see section 4.5).

Lithium

The combination of lithium and zofenopril / hydrochlorothiazide is generally not recommended (see section 4.5).

Race

As with other ACE-inhibitors, zofenopril may be less effective in lowering blood pressure in black people than in non-blacks.

ACE-inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Pregnancy

ACE-inhibitors should not be initiated during pregnancy. Unless continued ACE-inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE-inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

HYDROCHLOROTHIAZIDE**Renal impairment**

In patients with renal disease, thiazides may increase azotaemia. Cumulative effects of this active substance may develop in patients with impaired renal function. If progressive renal impairment becomes evident, as indicated by a rising non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy.

Hepatic impairment

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustments of insulin or oral hypoglycaemic agents may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients.

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 hypochloreaemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with zofenopril may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).

Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and usually does not require treatment.

Thiazides may decrease urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism.

Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out test for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Lupus erythematosus

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Anti-doping test

Hydrochlorothiazide contained in this medication could produce a positive analytic result in an anti-doping test.

Other

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the

treatment. If re-administration of the diuretic is deemed necessary, it is recommended to protect the areas exposed to the sun or artificial UVA

ZOFENOPRIL/HYDROCHLOROTHIAZIDE COMBINATION

In addition to the warnings related to the monocomponents, the following should be observed:

Pregnancy

Zofenopril / Hydrochlorothiazide is not recommended during the first trimester of pregnancy (see section 4.6).

Patients with renal insufficiency

Considering the effect of zofenopril and hydrochlorothiazide in patients with impaired renal function, zofenopril / hydrochlorothiazide should not be administered to patients with moderate to severe renal insufficiency (creatinine clearance < 45 ml/min).

Risk of hypokalaemia

The combination of an ACE-inhibitor with a thiazide diuretic does not rule out the occurrence of hypokalaemia. Regular monitoring of serum potassium should be performed.

Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

ZOFENOPRIL

CONCOMITANT USE NOT RECOMMENDED

Potassium sparing diuretics or potassium supplements: ACE-inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics *e.g.* spironolactone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of documented hypokalaemia they should be used with caution and with frequent monitoring of serum potassium and ECG (see section 4.4).

ACE-inhibitors, angiotensin II receptor blockers or aliskiren: 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 sections 4.3, 4.4 and 5.1).

CONCOMITANT USE REQUIRING CAUTION

Diuretics (thiazide or loop diuretics): Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with zofenopril (see section 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of zofenopril.

Anaesthetic medicinal products: ACE-inhibitors may enhance the hypotensive effects of certain anaesthetic medicinal products.

Narcotic/tricyclic antidepressants/antipsychotics/barbiturates: Postural hypotension may occur.

Other antihypertensive substances (e.g. beta-blockers, alpha-blockers, calcium antagonists): There may be additive hypotensive effect or potentiation. Treatment with nitroglycerine and other nitrates, or other vasodilators, should be used with caution.

Cimetidine: May enhance the risk of hypotensive effect.

Cyclosporin: Increased risk of renal dysfunction when ACE-inhibitors are used concurrently.

Allopurinol, procainamide, cytostatic or immunosuppressive agents: Increased risk of hypersensitivity reactions when ACE-inhibitors are used concurrently. Data from other ACE-inhibitors indicate an increased risk of leucopenia when used concurrently.

Antidiabetics: Rarely ACE-inhibitors can potentiate the blood glucose-reducing effects of insulin and oral antidiabetics like sulfonylurea, in diabetics. In such cases it may be necessary to reduce the dose of the antidiabetic during simultaneous treatment with ACE-inhibitors.

Haemodialysis with high-flux dialysis membranes: Increased risk of anaphylactoid reactions when ACE-inhibitors are used concurrently.

Sympathomimetics: May reduce the antihypertensive effects of ACE-inhibitors; patients should be carefully monitored to confirm that the desired effect is being obtained.

Antacids: Reduce the bioavailability of ACE-inhibitors.

Food: May reduce the rate but not the extent of absorption of zofenopril.

Gold: Nitritoid reactions (symptoms of vasodilation 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.

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)

Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (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).

Additional information

CYP enzymes: direct clinical data on the interaction of zofenopril with other active substances which are metabolised by CYP enzymes are not available. However, *in vitro* metabolic studies with zofenopril demonstrated no potential interaction with drugs that are metabolised by CYP enzymes.

HYDROCHLOROTHIAZIDE

CONCOMITANT USE REQUIRING CAUTION

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Sulfonamide diuretics should be taken at least one hour before or four to six hours after these medications.

Corticosteroids, ACTH, amphotericin B (parenteral), carbenoxolone, stimulant laxatives: There may be intensified electrolyte depletion, particularly hypokalaemia when administered concomitantly with Hydrochlorothiazide.

Calcium salts: Increased serum calcium levels due to decreased excretion may occur when administered concurrently with thiazide diuretics.

Cardiac glycosides: Thiazide induced hypokalaemia or hypomagnesaemia favours the occurrence of digitalis induced cardiac arrhythmia.

Medicinal products associated with torsade de pointes: Because of the risk of hypokalaemia, caution should be used when hydrochlorothiazide is co-administered with medicinal products associated with torsade de pointes, *e.g.* some antiarrhythmics, some antipsychotics, and other medicinal products known to induce torsade de pointes.

Pressor amines (*e.g.* adrenaline): Possible decreased response to pressor amines, but not sufficient to preclude their use with hydrochlorothiazide.

Skeletal muscle relaxants, non-depolarising (*e.g.* tubocurarine): Possible increased responsiveness to the muscle relaxant when used with hydrochlorothiazide.

Amantadine: Thiazide may increase the risk of undesirable effects caused by amantadine.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone, allopurinol): Dosage adjustment of uricosuric medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol.

Additional information

Laboratory test interactions: Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function.

ZOFENOPRIL/HYDROCHLOROTHIAZIDE COMBINATION

In addition to the interactions related to the monocomponents, the following should be observed:

CONCOMITANT USE NOT RECOMMENDED

Lithium: Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE-inhibitors.

Therefore, zofenopril / hydrochlorothiazide is not recommended in association with lithium and careful monitoring of serum lithium levels should be performed if the combination proves necessary.

Clinical Chemistry: Thiazides may decrease serum PBI (Protein Bound Iodine) levels without signs of thyroid disturbance.

CONCOMITANT USE REQUIRING CAUTION

Non-Steroidal Anti-Inflammatory medicinal product (including ASA \geq 3g/day): The administration of non-steroidal anti-inflammatory agents may reduce the antihypertensive effect of ACE-inhibitors and diuretics. Furthermore, it has been described that NSAIDs and ACE-inhibitors exert an additive effect on the increase in serum potassium whereas renal function may decrease. These effects are in principle reversible, and occur especially in patients with impaired renal function. Rarely, acute renal failure may occur, particularly in patients with compromised renal function such as the elderly or dehydrated.

Alcohol: Enhances the hypotensive effect of ACE-and hydrochlorothiazide.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Zofenopril and HCTZ

Given the effects of the individual components in this combination product on pregnancy, the use of zofenopril / hydrochlorothiazide is not recommended during the first trimester of pregnancy (see section 4.4). The use of zofenopril / hydrochlorothiazide is contraindicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4).

Zofenopril

The use of ACE-inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE-inhibitors is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE-inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE-inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE-inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE-inhibitor therapy during the second and third trimester is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3.) Should exposure to ACE-inhibitor have occurred from the second trimester of

pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE-inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Hydrochlorothiazide

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding

Zofenopril and HCTZ

The use of Zofenopril / Hydrochlorothiazide Mylan during breast-feeding is not recommended.

Zofenopril

Because no information is available regarding the use of zofenopril during breastfeeding, zofenopril is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of zofenopril / hydrochlorothiazide during breast-feeding is not recommended. If zofenopril / hydrochlorothiazide is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be remembered that occasionally drowsiness, dizziness or weariness may occur.

4.8 Undesirable effects

In controlled clinical trials involving 597 patients randomised to receive zofenopril plus Hydrochlorothiazide, no adverse reactions peculiar to this combination product have been observed. Adverse reactions have been limited to those that were reported previously with zofenopril calcium or hydrochlorothiazide. The incidence of undesirable effects showed no correlation with gender or age of the patients.

The table below shows all the adverse reactions that have been reported during clinical trials as at least probably- possibly related to treatment with zofenopril / hydrochlorothiazide 30/12.5. They are listed by body-system and ranked under headings of frequency using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$) or not known (frequency cannot be estimated from the available data).

Infections and infestations	
Uncommon:	Infection, bronchitis, pharyngitis
Metabolism and nutrition disorders	
Uncommon:	Hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hypokalaemia, hyperkalaemia, hyperuricaemia.
Psychiatric disorders	
Uncommon:	Insomnia
Nervous system disorders	
Common:	Dizziness, headache
Uncommon:	Somnolence, syncope, hypertonia
Cardiac disorders	
Uncommon:	Angina pectoris, atrial fibrillation, myocardial infarction, palpitations
Vascular disorders	
Uncommon:	Flushing, hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	
Common:	Cough
Uncommon:	Dyspnoea
Gastrointestinal disorders	
Uncommon:	Nausea, dyspepsia, gastritis, gingivitis, dry mouth, abdominal pain
Skin and subcutaneous tissue disorders	
Uncommon:	Angioedema, psoriasis, acne, dry skin, pruritus, Urticaria
Musculoskeletal and connective tissue disorders	
Uncommon:	Back pain
Renal and urinary disorders	
Uncommon:	Polyuria
Reproductive system and breast disorders	
Uncommon	Erectile dysfunction
General disorders and administration site conditions	
Uncommon:	Asthenia, influenza like illness, oedema peripheral.
Investigations	
Uncommon	Creatinine increase, liver function tests abnormal

Additional information on individual component:

Adverse reactions known to occur with each component given as monotherapy may occur during treatment with Zofenopril / Hydrochlorothiazide Mylan:

Zofenopril

The most common undesirable effects typical of ACE-inhibitors occurred in clinical trials in patients treated with zofenopril were the following:

Nervous system disorders	
Common	Dizziness, headache
Respiratory, thoracic and mediastinal disorders	
Common	Cough
Gastrointestinal disorders	
Common	Nausea/Vomiting
Skin and subcutaneous tissue disorders	
Uncommon	Rash
Rare	Angioedema
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle spasms
General disorders and administration site conditions	
Common	Fatigue
Uncommon	Asthenia

The following adverse reactions have been observed associated with ACE-inhibitors therapy:

Blood and lymphatic system disorders

In a few patients agranulocytosis and pancytopenia may occur.

There are reports of haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase deficiency.

Endocrine disorders

Not known, inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders

Very rare hypoglycaemia.

Psychiatric disorders

Rarely, depression, mood altered, sleep disorders, confusional state.

Nervous system disorders

Occasionally paraesthesia, dysgeusia, balance disorder.

Eye disorders

Rarely, vision blurred.

Ear and labyrinth disorders

Rarely, tinnitus.

Cardiac disorders

Individual cases of tachycardia, palpitations, arrhythmias, angina pectoris, myocardial infarction have been reported for ACE-inhibitors in association with hypotension.

Vascular disorders

Severe hypotension has occurred after initiation or increase of therapy. This occurs especially in certain risk groups (see section 4.4). In association with hypotension, symptoms like dizziness, feeling of weakness, impaired vision, rarely with disturbance of consciousness (syncope).

Rarely flushing occurs.

Respiratory, thoracic and mediastinal disorders

Rarely dyspnoea, sinusitis, rhinitis, glossitis, bronchitis and bronchospasm have been reported. ACE-inhibitors have been associated with the onset of angioneurotic oedema in a small subset of patients involving the face and oropharyngeal tissues. In isolated cases angioneurotic oedema involving the upper airways has caused fatal airway obstruction.

Gastrointestinal disorders

Occasionally, abdominal pain, diarrhoea, constipation and dry mouth can occur.

Individual cases of pancreatitis and ileus have been described in association with ACE-inhibitors.

Very rare small bowel angioedema.

Hepatobiliary disorders

Individual cases of cholestatic jaundice and hepatitis have been described in association with ACE-inhibitors.

Skin and subcutaneous tissue disorders

Occasionally allergic and hypersensitivity reactions can occur like pruritus, urticaria, erythema multiforme, Stevens- Johnson syndrome, toxic epidermic necrolysis, psoriasis-like efflorescences, alopecia.

This can be accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased ANA-titers. Rarely hyperhidrosis occurs.

Musculoskeletal and connective tissue disorders

Occasionally, myalgia can occur.

Renal and urinary disorders

Renal insufficiency may occur or be intensified. Acute renal failure has been reported (see section 4.4).

Rarely micturition disorders occur.

Reproductive system and breast disorders

Rarely, erectile dysfunction.

General disorders and administration site conditions

Very rarely oedema peripheral and chest pain.

Investigations

Increases in blood urea and creatinine, reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension.

In a few patients, decreases in haemoglobin, haematocrit, platelets and white-cell count have been reported. Increases in serum levels of hepatic enzymes and bilirubin have also been reported.

Hydrochlorothiazide

The adverse events reported that have been reported with the use of hydrochlorothiazide alone include the following:

Blood and lymphatic system disorders

Leukopenia, neutropenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow failure.

Immune system disorders

Anaphylactic reaction.

Metabolism and nutrition disorders

Anorexia, dehydration, gout, diabetes mellitus, metabolic alkalosis, hyperuricaemia, electrolyte imbalance (including hyponatraemia, hypokalaemia, hypomagnesaemia, hypochloraemia, hypercalcaemia), hyperglycaemia, hyperamylasaemia.

Psychiatric disorders

Apathy, confusional state, depression, nervousness, restlessness, sleep disorder.

Nervous system disorders

Convulsions, depressed level of consciousness, coma, headache, dizziness, paraesthesia, paresis.

Eye disorders

Xanthopsia, blurred vision, myopia (aggravated), lacrimation decreased.

Ear and labyrinth disorders

Vertigo.

Cardiac disorders

Cardiac arrhythmias, palpitations.

Vascular disorders

Orthostatic hypotension, thrombosis, embolism, shock.

Respiratory, thoracic and mediastinal disorders

Pneumonitis, interstitial lung disease, pulmonary oedema.

Gastrointestinal disorders

Dry mouth, nausea, vomiting, stomach discomfort, diarrhoea, constipation, abdominal pain, ileus paralytic, flatulence, sialoadenitis, pancreatitis.

Hepatobiliary disorders

Jaundice cholestatic, cholecystitis.

Skin and subcutaneous tissue disorders

Pruritus, purpura, urticaria, photosensitivity reactions, rash, cutaneous lupus erythematosus, vasculitis necrotising, toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders

Muscle spasm, myalgia.

Renal and urinary disorders

Renal impairment, renal failure acute, interstitial nephritis, glycosuria.

Reproductive system and breast disorders

Erectile dysfunction.

General disorders and administration site conditions

Asthenia, pyrexia, fatigue, thirst.

Investigations

Electrocardiogram change, blood cholesterol increased, blood triglycerides increased.

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 via [to be completed nationally with the national reporting system listed in [Appendix V](#)].

4.9 Overdose

Symptoms of overdosage are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure. Treatment is symptomatic and supportive. After ingestion of an overdose, the patients should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently.

Therapeutic measures depend on the nature and severity of the symptoms. If the ingestion is recent, measures to prevent absorption such as gastric lavage and administration of adsorbents and sodium sulfate may be implemented.

If hypotension occurs, the patient should be placed in shock position and the judicious use of volume expanders and/or treatment with angiotensin II considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered. ACE-inhibitors may be removed from the circulation by haemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

Overdosage with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdosage are nausea and somnolence. Hypokalaemia may result in muscle spasm and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE-inhibitors and diuretics, ATC code: C09BA15

Zofenopril / Hydrochlorothiazide Mylan is a fixed dose combination product containing zofenopril, an inhibitor of angiotensin converting enzyme (ACE) and hydrochlorothiazide, a thiazide diuretic. Both components have complementary modes of action and exert an additive antihypertensive effect.

Mechanism of action

Zofenopril is a sulfhydryl ACE-inhibitor able to block the enzyme that catalyses the conversion of angiotensin I to the vasoconstrictor peptide angiotensin II, which leads to decreased vasopressor activity and to reduced aldosterone secretion. This latter decrease may result in an increase in serum potassium concentration, along with sodium and fluid loss. The cessation of the negative feedback of angiotensin II on the renin secretion results in an increase of the plasma renin activity.

The mechanism through which zofenopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system. ACE is identical to kininase II, an enzyme that degrades bradykinin, a potent vasodilatory peptide, that seems play a role in the therapeutic effect of ACE-inhibitors.

Hydrochlorothiazide is a diuretic and antihypertensive agent. It affects the distal renal tubular mechanism of electrolyte reabsorption.

Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of zofenopril tends to reverse the potassium lost associated with these diuretics. With hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Clinical efficacy and safety

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group

5.2 Pharmacokinetic properties

Concomitant administration of zofenopril and hydrochlorothiazide has little or no effect on the bioavailability of either active substance. The combination tablet is bioequivalent to concomitant administration of the separate entities.

ZOFENOPRIL

Zofenopril is a prodrug, since the active inhibitor is the free sulfhydryl compound, zofenoprilat, resulting from thioester hydrolysis.

Absorption

Zofenopril is rapidly and completely absorbed by the oral route and undergoes nearly complete conversion to zofenoprilat, which reaches peak blood levels after 1.5 h following an oral dose of zofenopril. Single dose kinetics are linear over a dose-range of 10-80 mg of zofenopril and no accumulation occurs after the administration of 15-60 mg of zofenopril for 3 weeks.

The presence of food in the gastrointestinal tract reduces the rate but not the extent of absorption and the AUCs of zofenoprilat are nearly identical in the fasted or fed state.

Distribution

Approximately 88% of the circulating radioactivity measured *ex-vivo* following a radiolabelled dose of zofenopril is bound to plasma protein and the steady state volume of distribution is 96 litres.

Biotransformation

Eight metabolites, accounting for 76% of the urinary radioactivity, were identified in human urine following a radiolabelled dose of zofenopril. The main metabolite is zofenoprilat (22%), which is metabolised through several pathways, including glucuronide conjugation (17%), cyclization and glucuronide conjugation (13%), cysteine conjugation (9%) and S-methylation of the thiol group (8%).

Elimination

Radiolabelled zofenoprilat administered intravenously is eliminated in urine (76%) and faeces (16%) while following an oral dose of radiolabelled zofenopril, 69% and 26% of the radioactivity is recovered in urine and faeces respectively, indicating a dual route of

elimination (kidney and liver). Half-life of zofenoprilat is 5.5 h and its total body clearance is 1,300 ml/min following oral zofenopril.

Pharmacokinetics in older people

In older people, no dose adjustment is required when the renal function is normal.

Pharmacokinetics in renal dysfunction

Based on comparison of key pharmacokinetic parameters of zofenoprilat measured after oral administration of radiolabelled zofenopril, patients with mild renal impairment (creatinine clearance > 45 and < 90 ml/min) eliminate zofenopril from the body at the same rate as normal subjects (creatinine clearance > 90 ml/min).

In patients with moderate to severe renal impairment (7-44 ml/min), the rate of elimination is reduced to about 50% of normal.

In patients with end stage renal disease on haemodialysis and peritoneal dialysis, the rate of elimination is reduced to 25% of normal.

Pharmacokinetics in hepatic dysfunction

In patients with mild to moderate hepatic dysfunction given single doses of radiolabelled zofenopril, the C_{max} and T_{max} values for zofenoprilat were similar to those in normal subjects. However, AUC values in cirrhotic patients were about twice those obtained for normal subjects, indicating that the initial dose of zofenopril for patients with mild to moderate hepatic dysfunction should be half of that for patients with normal hepatic function.

There are no pharmacokinetic data of zofenopril and zofenoprilat in patients with severe hepatic dysfunction, therefore zofenopril is contraindicated in these patients.

HYDROCHLOROTHIAZIDE

Absorption

Hydrochlorothiazide is well absorbed (65 to 75 %) following oral administration. Plasma concentrations are linearly related to the administered dose.

The absorption of hydrochlorothiazide is dependent on intestinal transit time, being increased when the intestinal transit time is slow for example when given with food. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours and peak plasma levels were observed within 1 and 5 h after dosing.

Distribution

The thiazides are widely distributed in body fluids and are extensively (92%) bound to plasma proteins, particularly so to albumin, the substituted molecules being the most highly bound. This results in a lower renal clearance than the earlier compounds and in a more prolonged duration of action. No relationship has been demonstrated between hydrochlorothiazide plasma levels and the degree of reduction of blood pressure.

Elimination

Hydrochlorothiazide is eliminated primarily by renal pathway. Most of thiazide is excreted in the urine unchanged and more than 95% of hydrochlorothiazide appears unchanged in the

urine within 3-6 hours after an oral dose. In patients with renal disease, plasma concentrations of hydrochlorothiazide are increased and elimination half-life is prolonged. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

5.3 Preclinical safety data

The fixed combination zofenopril / hydrochlorothiazide revealed no special risks for human use, based on acute toxicity, repeated dose toxicity and genotoxicity studies.

Reproductive toxicity of the combination has been studied in rats and rabbits and zofenopril and hydrochlorothiazide did not show to be teratogenic. However in pregnant rats and rabbits the combination markedly increased the maternal toxicity induced by zofenopril alone.

Carcinogenicity studies were not performed with the combination zofenopril / hydrochlorothiazide.

Carcinogenicity studies conducted in mice and rats with zofenopril alone revealed no evidence of carcinogenicity.

Preclinical data of hydrochlorothiazide reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cellulose, microcrystalline
Lactose monohydrate
Maize starch, pregelatinised
Silica, colloidal anhydrous
Magnesium stearate

Film coat:

Lactose monohydrate
Hypromellose
Titanium dioxide (E171)
Macrogol 400
Iron oxide yellow (E172)
Iron oxide red (E172)
Iron oxide black (E172)
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White opaque PVC/PVdC/Aluminium blister pack sizes: 28

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: [To be completed nationally]

Date of latest renewal: [To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]