1.3.1.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

MYLAN CAPTOPRIL 12,5 (tablets)

MYLAN CAPTOPRIL 25 (tablets)

MYLAN CAPTOPRIL 50 (tablets)

2 QUALITIVE AND QUANTITIVE COMPOSITION

(Captopril: D-3-mercapto-2-methylpropanoyl-L-proline)

Each MYLAN CAPTOPRIL 12,5 mg tablet contains captopril 12,5 mg

Contains sugar: Lactose anhydrous 12,5 mg

Each MYLAN CAPTOPRIL 25 mg tablet contains captopril 25 mg

Contains sugar: Lactose anhydrous 25 mg

Each MYLAN CAPTOPRIL 50 mg tablet contains captopril 50 mg

Contains sugar: Lactose anhydrous 50,0 mg

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

MYLAN CAPROPRIL 12,5 mg: White capsule-shaped tablet with a partial bisect and “G” on one side and partial bisect and “C 12,5” on the other.

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MYLAN CAPROPRIL 25 mg: White, round, biconvex tablets with “C 25” on one side and quadrisected on the other side.

MYLAN CAPROPRIL 50 mg: White oval biconvex tablets approximately 11,3 mm by 5,8 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- MYLAN CAPTOPRIL is indicated for the treatment of mild to moderate hypertension in adult patients.
- It may be used alone or in combination with other antihypertensive medicines, especially thiazide-type diuretics. The blood pressure lowering effects of MYLAN CAPTOPRIL and thiazides are additive.
- MYLAN CAPTOPRIL is indicated for the treatment of patients with congestive heart failure who have not responded adequately to, or cannot be controlled by conventional therapy with diuretics and/or digitalis and in whom vasodilation is indicated.
- MYLAN CAPTOPRIL has been used with diuretics and digitalis.

4.2 Posology and method of administration

Posology

- The medicine should be taken 1 hour before meals.
- The recommended initial dosage for adults is 25 mg two or three times a day.
- This is increased as necessary, after 2 weeks to 50 mg three times daily.
- The maximum daily dosage should not exceed 150 mg daily.

Congestive heart failure:

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- MYLAN CAPTOPRIL therapy must be started under close medical supervision.
- It should be added to conventional therapy with diuretic (and digitalis where indicated). A much smaller dosage, 6,25 mg - 12,5 mg, three times daily is appropriate for the initiation of therapy in patients with heart failure, or in others who have received intensive therapy with diuretics.

Special populations

Renal impairment:

- Reduced dosage is also indicated for patients with impaired renal function.
- After the desired therapeutic effect has been achieved, the total daily dose should be reduced, or the dose intervals increased.

The following maximum daily doses are suggested as a guide to minimise accumulation:

Creatinine clearance **(mℓ/min/1,75 mm^3)**	**Maximum total daily dose** **(mg)**
more than 80	450
80-41	300
40-21	150
20-11	75
less than 10	37,5

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to the active substance captopril or to any of the excipients of MYLAN CAPTOPRIL.

- Patients with a history of angioedema related to previous ACE-inhibitor therapy or angiotensin receptor blocker (ARBs). These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Aortic stenosis.
- Hypertrophic obstructive cardiomyopathy (HOCM) (*see section 4.4*).
- Severe renal function impairment (creatinine clearance below 30 ml/min).
- Bilateral renal stenosis or renal artery stenosis in patients with a single kidney.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (*see section 4.5).*
- Porphyria.
- Lithium therapy: Concomitant administration with MYLAN CAPTOPRIL may lead to toxic blood concentration of lithium *(see section 4.5)*.
- Pregnancy and lactation (*see section 4.6*).
- The concomitant use of MYLAN CAPTOPRIL with aliskiren-containing products is contraindicated *(see section 4.4 and 4.5)*.
- Concomitant use of fluoroquinolones with ACE inhibitors/Renin-Angiotensin blockers is contraindicated in patients with moderate to severe renal impairment.
- Concomitant use with sacubitril/valsartan therapy. MYLAN CAPTOPRIL must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (*see section 4.4 and 4.5).*

4.4 Special warnings and precautions for use

MYLAN CAPTOPRIL should be used with caution in the following conditions:

Pregnancy:

Should a woman become pregnant while receiving MYLAN CAPTOPRIL, the treatment must be stopped promptly and switched to a different antihypertensive medicine (*see section 4.3 & 4.6*).

- If a woman is contemplating pregnancy, a different class of medicine should be used (*see section 4.6*).
- ACE-inhibitors pass through the placenta and can be presumed to cause disturbances in foetal blood pressure regulatory mechanisms. Oligohydramnios, as well as hypotension, oliguria and anuria in newborns have been reported after administration of ACE-inhibitors such as MYLAN CAPTOPRIL in the second and third trimesters.
- Cases of defective skull ossification have been observed.
- Prematurity and low birth mass can occur.

Cerebrovascular disease or ischaemic heart disease:

- Reduction in blood pressure could aggravate these conditions and may result in myocardial infarction and cerebrovascular accidents.
- Myocardial infarction and cerebrovascular accidents may be due to severe fall in blood pressure in high-risk patients, e.g. those with ischaemic heart disease or cerebrovascular disease.
- In volume depleted patients or patients with ischaemic heart disease or cerebrovascular disease, therapy should be monitored, especially when the dose of MYLAN CAPTOPRIL or diuretic is adjusted (see sub-header '*Volume depleted patients***'.**)
- If hypotension occurs, the patient should be placed in the supine position, and if necessary, receive an intravenous infusion of 0,9 % saline.

Volume depleted patients (e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting):

- Although it may occur in normo volumic patients, hypotension is more likely in volume depleted patients.
- A sudden reduction in angiotensin II may result in sudden and severe hypotension. There is also an increased risk of MYLAN CAPTOPRIL induced renal failure, especially in those with congestive heart failure.
- Patients at a high risk of symptomatic hypotension, e.g., patients with salt or volume depletion, with or without hyponatraemia, should have these conditions corrected before therapy with MYLAN CAPTOPRIL. Monitoring is required after initiating therapy.

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 MYLAN CAPTOPRIL and aliskiren is therefore contraindicated *(see section 4.3*).
- MYLAN CAPTOPRIL should not be used concomitantly with aliskiren *(see section 4.3*)

Hypotension in acute myocardial infarction:

- Treatment with MYLAN CAPTOPRIL must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator.

- These include patients with systolic blood pressure of 100 mmHg or lower or cardiogenic shock.
- During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mmHg or lower.
- Maintenance doses should be reduced to 5 mg or temporarily to 2,5 mg if systolic blood pressure is 100 mmHg or lower.
- If hypotension persists (systolic blood pressure less than 90 mmHg or more than 1 hour) then MYLAN CAPTOPRIL should be withdrawn.
- In acute myocardial infarction, treatment with MYLAN CAPTOPRIL should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 micromol/l or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 micromol/l or doubling of the pre-treatment value) then MYLAN CAPTOPRIL may need to be withdrawn *(see section 4.3*).
- In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.

Bone marrow depression:

- Increased risk of agranulocytosis and neutropaenia.

Diabetic patients:

- Diabetes mellitus – Increased risk of hyperkalaemia, as well as hypoglycaemia may occur.

Hyperkalaemia:

- MYLAN CAPTOPRIL may cause an increase in serum potassium levels.

- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene and amiloride is contraindicated (*see section 4.3)*. Concomitant use may lead to hyperkalaemia, which may be severe and lead to cardiac conduction abnormalities, dysarrythmias and cardiac arrest (*see section 4.5*).
- Diabetics, and elderly diabetics particularly, may be at increased risk of hyperkalaemia. It is recommended that patients taking an ACE inhibitor, such as MYLAN CAPTOPRIL, should have serum electrolytes (including potassium, sodium, and urea) measured frequently.

Renovascular disease:

- MYLAN CAPTOPRIL should not be used in patients with renovascular disease or suspected renovascular disease, but it may be used cautiously in severe resistant hypertension in such patients. In this instance MYLAN CAPTOPRIL should only be used under specialist supervision.
- The elderly and patients with peripheral vascular diseases or generalised atherosclerosis may have asymptomatic renovascular disease.
- Increases in blood urea and serum creatinine have been seen in patients with no apparent pre-existing vascular disease, especially when MYLAN CAPTOPRIL has been given concomitantly with a diuretic. Dosage reduction or discontinuation of MYLAN CAPTOPRIL or the diuretic may be required.

Renal artery stenosis:

- Renal artery stenosis, bilateral or in one kidney or renal transplant – Increased risk of renal function impairment which may lead to an increase in blood urea and serum creatinine concentrations which may be reversible upon discontinuation of therapy.

- There is also an increased risk of agranulocytosis and neutropaenia when immunosuppressants are concurrently administered (*see sub-header 'Neutropenia/Agranulocytosis'*).

Renal function impairment:

- Concomitant use of fluoroquinolones and ACE inhibitors/renin-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/renin-angiotensin receptor blockers.
- Decreased elimination of MYLAN CAPTOPRIL resulting in an increased risk of hyperkalaemia. These patients may require lower doses (*see sub-header 'Hyperkalaemia'*).

Anaphylactoid reactions during desensitisation:

- Anaphylactoid reactions have occurred in patients using ACE inhibitors, including MYLAN CAPTOPRIL during desensitising protocols involving for example, hymenoptera venom.

Anaphylactoid reactions during high-flux dialysis / lipoprotein apheresis membrane exposure:

- Anaphylactoid reactions have been reported in patients exposed to either high-flux membrane dialysis or low-density lipoprotein apheresis with dextran sulfate absorption.

Hypersensitivity/Angioedema:

- If angioedema of the face, extremities, lips, tongue, glottis and/or larynx is observed in patients treated with MYLAN CAPTOPRIL, MYLAN CAPTOPRIL should be discontinued promptly. These patients should be monitored to ensure complete resolution of 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. This may include the administration of adrenaline and/or the maintenance of a patient's airway.
- The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.
- **These patients should never receive any MYLAN CAPTOPRIL, ACE-inhibitors or angiotensin-receptor blockers again.**
- Concomitant use of ACE inhibitors with sacubitril/valsartan is not recommended due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of captopril. Treatment with MYLAN CAPTOPRIL must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (*see sections 4.3 and 4.5*).
- Intestinal angioedema may occur in patients treated with MYLAN CAPTOPRIL with symptoms such as abdominal pain (with or without nausea or vomiting).
- Patients receiving coadministration of an ACE inhibitor such as MYLAN CAPTOPRIL and mTOR (mammalian target of rapamycin) inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy or vildagliptin may be at increased risk for angioedema (*see section 4.5*).

- **Ethnic differences:**

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MYLAN CAPTOPRIL causes a higher rate of angioedema in black patients than in non-black patients.

Surgery/Anaesthesia:

- In patients undergoing major surgery or during anaesthesia with ~~agents~~ medicines that produce hypotension, MYLAN CAPTOPRIL may block angiotensin II formation secondary to complementary rennin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Neutropenia/Agranulocytosis:

MYLAN CAPTOPRIL should be used with caution in the following conditions:

- Autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma, increase the risk for development of neutropaenia or agranulocytosis.
- All patients receiving MYLAN CAPTOPRIL should be instructed to report any signs of infection (e.g.: sore throat or fever) to their doctor.
- If MYLAN CAPTOPRIL is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately two-week intervals for about three months, then periodically *(see sub-header 'Renal artery stenosis'*).

Proteinuria:

- Patients with prior renal disease or those receiving MYLAN CAPTOPRIL should have urinary protein estimations (dipstick on first morning urine) prior to treatment, and periodically thereafter.

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Anaemia:

- Anaemia with reduced haemoglobin levels was reported in renal transplants or haemodialysis patients. Anaemia does not appear to be dose-dependent, however it is linked to ACE inhibitors mechanism of action. It is reversible upon MYLAN CAPTOPRIL discontinuation.

Cough:

- A persistent dry (non-productive) cough may occur with MYLAN CAPTOPRIL.

Use in hepatic impairment:

- Patients receiving MYLAN CAPTOPRIL who develop jaundice or marked elevations of hepatic enzymes should discontinue MYLAN CAPTOPRIL.

Effects on laboratory tests:

- MYLAN CAPTOPRIL may cause a false-positive urine test for acetone.

Paediatric Population:

- Safety and efficacy in children have not been established.

Lactose warning:

MYLAN CAPTOPRIL contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take MYLAN CAPTOPRIL.

4.5 Interaction with other medicines and other forms of Interaction

Concomitant use of MYLAN CAPTOPRIL with:

Diuretics, alcohol, anti-hypertensive and other hypotension-producing medicines:

- The antihypertensive effect is additive.
- Dosage adjustments may be necessary during concurrent use or when one medicine is discontinued.
- **Medicines affecting sympathetic activity:**

  The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving MYLAN CAPTOPRIL alone or with diuretics.

  Therefore, medicines affecting sympathetic activity (e.g.: ganglionic blocking medicines or adrenergic neuron blocking medicines) should be used with caution.

Loop, thiazide or related diuretics:

- "First dose hypotension" may occur *(see section 4.2*).

Potassium supplements or potassium sparing diuretics:

- Potassium supplements or potassium sparing diuretics such as spironolactone, triamterene or amiloride is contraindicated (*see section 4.3)*. Concurrent administration may result in hyperkalaemia (*see section 4.4)*.

Combination with non-steroidal anti-inflammatory medicines (NSAIDs):

- When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory medicines (i.e., selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk

of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function.

- The combination should be administered with caution, especially in the elderly and in volume depleted patients. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.
- Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with MYLAN CAPTOPRIL.

Lithium*:*

- Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors.
- Use of MYLAN CAPTOPRIL with lithium is not recommended (*see section 4.3*).

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury *(see section 4.3).*

Dual blockade of the RAAS with ARBs, ACE inhibitors, 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 *(see section 4.3 & 4.4).*

Medicines with vasodilator activity:

- Glyceryl trinitrate or other nitrates (as used for management of angina) or other medicines with vasodilator activity should be discontinued before starting MYLAN CAPTOPRIL.

Haemodialysis membranes:

- Hypersensitivity-like (anaphylactoid) reactions have been reported with high-flux dialysis membranes (*see section 4.4*).

Mammalian Target of Rapamycin (mTOR) Inhibitors:

- Patients taking concomitant mTOR inhibitor (e.g., temsirolimus, sirolimus, everolimus) medicine may be at increased risk for angioedema.

Combination of ACE inhibitors and vildagliptin:

- Patients taking concomitant vildagliptin medicine may be at an increased risk of angioedema.

Combination of ACE inhibitors and sacubitril/valsartan:

- Concomitant use of MYLAN CAPTOPRIL with sacubitril/valsartan is not recommended as this increases the risk of angioedema (*see section 4.3)*.

Allopurinol, procainamide, cytostatic, or immuno-suppressive agents:

- Concomitant administration with MYLAN CAPTOPRIL may lead to an increased risk of leukopenia.

Tricyclic anti-depressants, neuroleptics, amifostine, baclofen:

- Co-administration of these medicines with MYLAN CAPTOPRIL may potentially increase antihypertensive effects and risk of postural hypotension.

Antidiabetics:

- MYLAN CAPTOPRIL can potentiate the blood glucose-reducing effects of insulin and oral antidiabetics such as sulphonylurea in diabetics.

Gold:

- Nitritoid reactions with symptoms such as flushing, dizziness, nausea, vomiting and drop in blood pressure up to circulatory collapse have been reported in patients treated with ACE inhibitors such as MYLAN CAPTOPRIL and injectable gold preparations (sodium aurothiomalate) at the same time.

4.6 Fertility, pregnancy and lactation

Pregnancy

- MYLAN CAPTOPRIL is contraindicated during pregnancy (*see section 4.3*).
- ACE-inhibitors, such as MYLAN CAPTOPRIL, can cause foetal morbidity and death.
- Pregnant women should be informed of the potential hazards to the foetus and **must not take MYLAN CAPTOPRIL** during pregnancy (*see section 4.3)*.
- Patients planning pregnancy should be changed to alternative anti-hypertensive medicines which have an established safety profile for use in pregnancy.
- When pregnancy is diagnosed, treatment with MYLAN CAPTOPRIL 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.

- MYLAN CAPTOPRIL 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 newborns, have been reported after administration of MYLAN CAPTOPRIL 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*).

Breastfeeding

- Safety in breastfeeding has not been established.

Fertility

- No information available.

4.7 Effects on ability to drive and use machines

MYLAN CAPTOPRIL may cause dizziness and have no or negligible influence on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.
Caution when driving or performing tasks requiring alertness because of possible dizziness.

4.8 Undesirable effects

MYLAN CAPTOPRIL tablets can have undesirable effects.

Tabulated list of adverse reactions

Body system	Frequent	Less frequent

Blood and the lymphatic system disorders:		Decrease in white blood cell count, haemoglobin and haemotocrit, bone marrow suppresion, anaemia, thrombocytopaenia, haemolytic anaemia, agranulocytosis, neutropenia, eosinophilia, pancytopenia, auto-immune disease
Immune system disorders:		Hypersensitivity /angioedema reactions -serious or life-threatening (*see section 4.4)*, serum sickness-like syndrome
Metabolism and nutrition disorders:		Hyperkalaemia, hyponatraemia, hypoglycaemia
Psychiatric disorders:	Mood alterations, sleep disorders, mental confusion	
Nervous system disorders:	Dizziness	Headache, fatigue, paraesthesia, vertigo, malaise, drowsiness
Eye disorders:		Disturbed vision, itching and/or dry eyes
Cardiac disorders:		Orthostatic effects (including hypotension, myocardial infarction,

		cerebrovascular accident, tachycardia, palpitations, schest pain, angina pectoris, Raynaud's phenomenon and congestive heart failure, cardiac arrest, rhythm disturbances/orthostatic hypotension, syncope
Respiratory, thoracic and mediastinal disorders:	Cough	Bronchospasm, sinusitis, rhinitis, dyspnoea
Gastrointestinal disorders:	Diarrhoea, nausea, abdominal pain, indigestion, dry mouth, vomiting, taste disturbances	Glossitis, pancreatitis, intestinal angioedema and constipation, stomatitis, aphthous ulcers, tongue ulceration, peptic ulcer and a scalded sensation of the oral mucosa
Hepato-biliary disorders:		Hepatitis (hepatocellular or cholestatic) jaundice, increases in serum bilirubin, increased liver enzymes
Skin and subcutaneous tissue disorders:		Photosensitivity or other dermatological manifestations may occur, diaphoresis, alopecia,

		psoriasis, severe skin disorders including bullous pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme, angioedema of the face, which may be fatal, extremities, lips, tongue, glottis and/or larynx, angio-oedema, rash, urticaria, pruritus, exfoliative dermatitis
Musculoskeletal, connective tissue and bone disorders:		Asthenia, myalgia
Renal and urinary disorders:		Ureamia, oliguria, anuria, renal dysfuntion, acute renal failure , proteinuria (*see section 4.4*), polyuria, increased urinary frequency, nephrotic syndrome and glomerulopathy
Reproductive system and breast disorders:		Impotence, loss of libido, gynecomastia

General disorders and administrative site conditions:		A symptom complex has been reported which may include: fever, vasculitis, positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis
Investigations:		Increased blood urea, increased blood creatinine, increased liver transaminases, alkaline phosphatase and serum bilirubin, increases in serum potassium (*see section 4.4)*

Post-marketing experience:

Body system	**Frequency not known**
Musculoskeletal, connective tissue and bone disorders:	Myasthenia
Psychiatric disorders:	Ataxia, confusion, depression, somnolence
Nervous system disorders:	Nervousness
Respiratory, thoracic and mediastinal disorders:	Eosinophilic pneumonitis, rhinitis

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As with other ACE inhibitors, a syndrome has been reported which may include fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated (erythrocyte sedimentation rate) ESR.

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. Healthcare 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

In overdose, undesirable effects can be precipitated and/or be of increased severity (*see section 4.8)*.

Symptoms of overdose:

Severe hypotension, electrolyte disturbances and renal failure.

Treatment of overdose:

- Treatment is supportive and symptomatic.
- Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion.
- Treatment consists of volume expansion to correct hypotension and treating dehydration and electrolyte imbalances.
- MYLAN CAPTOPRIL is removable by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1 Vasodilators, hypotensive medicine

Pharmacotherapeutic group and ATC code:

Agents acting on the renin-angiotensin system, ACE Inhibitors, plain

ATC Code: C09A A01

Captopril inhibits angiotensin I-converting enzyme (ACE) activity. It inhibits the conversion of the relatively inactive angiotensin I to the active angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone. Decreased angiotensin II levels result in a decrease in vasopressor activity and a reduction in aldosterone secretion, which may result in small increases in serum potassium.

It is also thought that ACE inhibition may inhibit degradation of bradykinin, leading to increased bradykinin levels.

Pharmacokinetic properties:

About 60 to 75 % of the dose of captopril is absorbed from the gastrointestinal tract and peak plasma concentrations are achieved within about an hour. Absorption has been reported to be reduced in the presence of food, but this may not be clinically relevant. Captopril is about 30 % bound to plasma proteins. It crosses the placenta and is found in breast milk at about 1 % of maternal blood concentrations. It is largely excreted in the urine, 40 to 50 % as unchanged medicine, the rest as disulfide and other metabolites. The elimination half-life has been reported to be 2 to 3 hours but this is increased in renal impairment. Captopril is removed by haemodialysis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, lactose anhydrous, maize starch, stearic acid and sodium starch glycollate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

MYLAN CAPTOPRIL 12,5:

24 months.

MYLAN CAPTOPRIL 25:

36 months.

MYLAN CAPTOPRIL 50:

36 months.

6.4 Special precautions for storage

Store below 25 °C.

Store well closed in a cool, dry place.

6.5 Nature and contents of container

MYLAN CAPTOPRIL 12,5:

White opaque high-density polypropylene container with a coated metal closure with liner and polystyrene foam inner seal. Pack size: 100

MYLAN CAPTOPRIL 25:

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White opaque high-density polypropylene container with a coated metal closure with liner and polystyrene foam inner seal.

Pack size: 30, 100

Not all pack sizes may be marketed.

MYLAN CAPTOPRIL 50:

White opaque high-density polypropylene container with a coated metal closure with liner and polystyrene foam inner seal.

Pack size: 100, 500

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused product or waste material should be disposed of in accordance with local requirements.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

1600

Republic of South Africa

8 REGISTRATION NUMBER(S)

MYLAN CAPTORPIL 12,5: 32/7.1/0545

MYLAN CAPTOPRIL 25: 29/7.1/0228

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MYLAN CAPTOPRIL 50: 32/7.1/0528

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 December 2009

10 DATE OF REVISION OF TEXT

27 September 2024