11/2015

**Vasodip® Combo**

A landmark in the field,

The brand of the Combo presents the following changes on its label and prescription:

**Vasodip® Combo**

The following sections are amended and constitute an enhancement:

4.1 Indication

 [...] 

*Fixed combination Vasodip Combo should not be used for initial treatment of hypertension.*

4.2 Posology, dosage & administration

*Fixed combination Vasodip Combo should not be used for initial treatment of hypertension.*

[...] 

4.3 Contraindications
Association with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR<60ml/min/1.73m2) (see section 4.5 and 5.1).

4.4 Special Warnings and Special Precautions for use

Symptomatic hypotension
Particularly careful monitoring is required with enalapril in:
- severe hypotension with systolic blood pressure less than 90 mmHg
- decompensated heart failure

Use in renal impairment
Particular caution is required with enalapril when initiating treatment in patients with mild to moderate renal impairment. Routine monitoring of serum potassium and creatinine under enalapril treatment is part of the normal medical care of these patients.
Reports of renal failure associated with the use of enalapril have been made especially in patients with severe heart failure or underlying renal disease, including renal artery stenosis.
If diagnosed promptly and treated appropriately, renal failure under enalapril treatment is usually reversible.
Some hypertensive patients with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when enalapril has been given concurrently with a diuretic. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying renal artery stenosis (see section 4.4, Renovascular hypertension).

Renovascular hypertension
Patients with bilateral renal artery stenosis or stenosis of the artery of a single functioning kidney are particularly at risk of developing hypotension or renal failure insufficiency under ACE-inhibitor therapy. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses and cautious titration and monitoring renal function.

Hepatic failure
The antihypertensive effect of lercanidipine can be potentiated in patients with hepatic dysfunction.
Rarely, ACE-inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis 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 elevation of hepatic enzymes should discontinue the ACE-inhibitor and receive appropriate medical follow up.

Hypersensitivity/angioneurotic oedema

In cases where the swelling was limited to the face and lips, symptoms generally resolved without treatment. However, antihistamines were useful in relieving the symptoms.
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. **Angioneurotic oedema with laryngeal involvement can be fatal.**

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery.

...**Hyperkalaemia**

An increase in serum potassium has been observed in some patients on ACE-inhibitors in enalapril. Risk factors for hyperkalaemia are: renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes as well as concurrent treatment with other drugs that can lead to an increase in serum potassium values (e.g. heparin).

If concomitant use of one of the above-mentioned substances is indicated, serum potassium should be regularly monitored.

The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of enalapril and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

**Lithium**

The combination of lithium and enalapril is generally not recommended (see section 4.5).

**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.

...**Other not recommended medications**

This medicinal product is generally not recommended in combinations with lithium, potassium-sparing diuretics, potassium supplements and estramustine (see 4.5)

**4.5 Interaction with Other Medicaments and Other Forms of Interaction**

**Lercanidipine**

...**Pediatric population**
Interaction studies have only been performed in adults.

**Enalapril maleate**

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

Some active substances or therapeutic classes may favour the development of hyperkalaemia: potassium salts, potassium-sparing diuretics, ACE-inhibitors, angiotensin II inhibitors, non-steroidal anti-inflammatory agents, heparins (low molecular weight or unfractionned), ciclosporin and tacrolimus, trimethoprim.

The occurrence of hyperkalaemia may depend on the existence of associated risk factors.

This risk is increased in combination with the above-mentioned medicinal products.

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).

**Not recommended combinations**

**Potassium-sparing diuretics and potassium supplements**

ACE-inhibitors attenuate diuretic-induced potassium loss. Potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes may lead to significant increases in serum potassium.

Non-steroidal anti-inflammatory drugs (NSAIDs) Including Selective Cyclooxygenase-2 (COX-2) Inhibitors

Chronic treatment with NSAIDs may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE-inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. This is usually reversible. Rarely, acute renal failure may occur, especially in patients with impaired renal function such as elderly or dehydrated patients.

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and others antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE-inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

The co-administration of NSAIDs (including COX-2 inhibitors) and angiotensin II receptor antagonists or ACE-inhibitors exert an additive effect on the increase in serum potassium, and
may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function (such as the elderly or patients who are volume-depleted, including those on diuretic therapy). Therefore, the combination should be administered with caution in patients with compromised renal function. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy and periodically thereafter.

Baclofen

Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.

Ciclosporin

Ciclosporin increases the risk of hyperkalaemia with ACE inhibitors.

Combinations to be taken into account

Amifostine

Increased antihypertensive effect.

Corticosteroids, tetracosaactide (systemic) (except hydrocortisone used as a substitute in Addison’s disease):

Reduced antihypertensive effect (corticosteroid-induced salt/volume retention).

Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide

Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.

Antacids

Antacids induce decreased bioavailability of ACE inhibitors.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE-inhibitors. A decreased response to pressor amines (e.g. adrenaline) is possible, but not sufficient to preclude their use.

4.6 Pregnancy and Fertility, Lactation

Pregnancy

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3). Maternal oligohydramnios, presumably representing decreased fetal renal function, has
occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development.

[...]

**For enalapril and lercanidipine in association**

There are no or limited amount of data from the use of enalapril maleate/lercanidipine HCl in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). **Vasodip Combo** should not be used in the second and third trimester of pregnancy. It is not recommended in the first trimester of pregnancy and in women of childbearing potential not using contraception.

[...]

**4.8 Adverse events**

**Summary of the safety profile**

The safety of Vasodip Combo has been evaluated in five double-blind controlled clinical studies and in two long term open-label extension phases. In total, 1,141 patients have received Vasodip Combo at a dose of 10 mg/10 mg, 20 mg/10 mg and 20 mg/20 mg. The undesirable effects observed with combination therapy have been similar to those already observed with one or the other of the constituents given alone. The most commonly reported adverse reactions during treatment with Vasodip Combo were cough (4.03%), dizziness (1.67%) and headache (1.67%).

[...]

**Adverse drug reactions observed with Vasodip Combo 10:**

**Immune system disorders:**

Uncommon: Hypersensitivity*

**Nervous system disorders:**

Common: Dizziness

Uncommon: Headache

**Ear and labyrinth disorders:**

Common: Vertigo, including vertigo positional

**Cardiac disorders:**

Uncommon: Palpitations, Tachycardia*

**Vascular disorders:**

Uncommon: Hypotension*, Circulatory collapse*

**Respiratory, thoracic and mediastinal disorders:**

Common: Cough

Uncommon: Dry throat*

**Gastrointestinal disorders:**

Uncommon: Abdominal pain upper*, Nausea*

**Skin and subcutaneous tissue disorders:**

Uncommon: Dermatitis*, Erythema*, Lip oedema*, Urticaria*

**Musculoskeletal and connective tissue disorders:**

Uncommon: Arthralgia*

**Renal and urinary disorders:**

Uncommon: Polyuria*, Polakiuria*

**Reproductive system and breast disorders:**

Uncommon: Erectile dysfunction*

**General disorders and administration site condition:**

Uncommon: Fatigue, Asthenia*
Investigations:
Uncommon: Hemoglobin decreased

Note: *in 1 patient only

In controlled clinical trials using the combination lercanidipine hydrochloride 10 mg/ enalapril maleate 20 mg and including 410 patients, undesirable effect were reported as shown in the following table.

Adverse drug reactions observed with Vasodip Combo 20:

Immune system disorders:
- Uncommon: Angioedema*

Blood and lymphatic system disorders:
- Uncommon: Thrombocytopenia

Metabolism and nutrition disorders:
- Uncommon: Hypertriglyceridaemia*
- Psychiatric disorders:
- Uncommon: Anxiety*

Nervous system disorders:
- Common: Headache, Dizziness (including dizziness postural)
- Cardiac disorders:
- Uncommon: Palpitations
- Vascular disorders:
- Common: Flushing
- Uncommon: Hypotension*

Respiratory, thoracic and mediastinal disorders:
- Common: Cough
- Uncommon: Pharyngolaryngeal pain*

Gastrointestinal disorders:
- Uncommon: Abdominal pain, Constipation*, Dyspepsia*, Nausea*, Tongue disorder*

Skin and subcutaneous tissue disorders:
- Uncommon: Erythema*, Rash*

Musculoskeletal and connective tissue disorders:
- Uncommon: Arthralgia*

Renal and urinary disorders:
- Uncommon: Nocturia*

General disorders and administration site condition:
- Common: Oedema peripheral
- Uncommon: Asthenia, Fatigue, Feeling hot*

Investigations:
- Uncommon: ALT increased, AST increased

Note: * in 1 patient only

**Blood and lymphatic system disorders**
- Uncommon: Thrombocytopenia
- Rare: Haemoglobin decreased

**Immune System Disorders**
- Rare: Hypersensitivity

**Metabolism and nutrition disorders**
- Uncommon: Hyperkalaemia

**Psychiatric disorders**
Uncommon: Anxiety

**Nervous system disorders**
Common: Dizziness, headache
Uncommon: Dizziness postural

**Ear and labyrinth disorders**
Uncommon: Vertigo
Rare: Tinnitus

**Cardiac Disorders**
Uncommon: Tachycardia, palpitations

**Vascular disorders**
Uncommon: Flushing, hypotension
Rare: Circulatory collapse

**Respiratory, thoracic and mediastinal disorders**
Common: Cough
Rare: Dry throat, oropharyngeal pain

**Gastrointestinal disorders**
Uncommon: Abdominal pain, constipation, nausea
Rare: Dyspepsia, lip oedema, tongue disorder, diarrhoea, dry mouth, gingivitis

**Hepatobiliary Disorders**
Uncommon: ALT increased, AST increased

**Skin and sub-cutaneous tissue disorders**
Uncommon: Erythema
Rare: Angioedema, swelling face, dermatitis, rash, urticaria

**Musculoskeletal, connective tissue disorders**
Uncommon: Arthralgia

**Renal and urinary disorders**
Uncommon: Pollakiuria
Rare: Nocturia, polyuria

**Reproductive System and Breast Disorders**
Rare: Erectile dysfunction

**Erectile dysfunction**

**General disorders and administration site conditions**
Uncommon: Asthenia, fatigue, feeling hot, oedema peripheral

Undesirable effects occurring in one patient only are reported under the frequency rare.

Additional information on the individual components

*Lercanidipine alone*

Adverse reactions occurred in approximately 1.8% of patients treated.

[...]

*Enalapril alone*

[...]*Endocrine disorders:*

Not known: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

[...]*Cardiac and vascular disorders:
Very common: dizziness*
Common: hypotension (including orthostatic hypotension), syncope, thoracic pain, rhythm disturbances, angina pectoris, tachycardia, chest pain.
Uncommon: palpitations, myocardial infarction or cerebrovascular accident*, possibly secondary to excessive hypotension in high-risk patients (see section 4.4)
Rare: Raynaud's phenomenon

* Incidence rates were comparable to those in the placebo and active control groups in the clinical trials.

Skin and subcutaneous tissue disorders:

Uncommon: erythema multiforme, Stevens-Johnson syndrome, dermatitis exfoliative, toxic epidermal necrolysis, pemphigus, erythroderma.

Reproductive system and breast disorders:

Uncommon: erectile dysfunction, impotence
Rare: gynaecomastia

General disorders and administration site conditions:

Very common: asthenia
Common: fatigue
Uncommon: muscle cramps malaise, tinnitus, flushing, fever

4.9 Overdose

Up to the present time, no cases of Vasodip Combo overdose have been reported.
The likeliest symptoms of overdose are severe hypotension, bradycardia, reflex tachycardia, shock, stupor, electrolyte disturbances and renal failure.

Management of overdose:
Treatment is principally directed towards elimination of the poison and restoration of stable cardiovascular conditions. Following oral ingestion, copious gastric lavage—possibly combined with intestinal irrigation—is indicated.

Experience with lercanidipine overdose
Symptoms:
As with other dihydropyridines, overdose might be expected to cause excessive peripheral vasodilatation with marked hypotension and reflex tachycardia.
In post-marketing experience, three cases of overdose have been reported (150 mg, 280 mg and 800 mg of lercanidipine respectively had been ingested in an attempt to commit suicide). The first
patient developed sleepiness. The second patient developed cardiogenic shock with severe myocardial ischaemia and mild renal failure. The third patient showed vomiting and hypotension. All patients recovered without sequelae.

Treatment:
In the above-mentioned cases, treatment consisted respectively in: gastric lavage; high-dose catecholamines, furosemide, digitalis and parenteral plasma expanders; activated charcoal, laxatives and intravenous dopamine.
In the case of severe hypotension, bradycardia and unconsciousness, cardiovascular support can be helpful, with intravenous atropine to counteract the bradycardia.
In view of the prolonged pharmacological action of lercanidipine, the cardiovascular status of patients who have taken an overdose must be monitored for at least 24 hours. There is no information on the value of dialysis. Since lercanidipine is highly lipophilic, it is very unlikely that plasma levels will be indicative of the duration of the risk phase. Dialysis may not be effective.

Experience with enalapril overdose
Limited data are available on overdose in humans.

Symptoms:
The most prominent features of overdose reported to date are marked hypotension (beginning some 6 hours after ingestion of the tablets), concomitant with blockage of renin-angiotensin system, and stupor. Symptoms associated with overdose of ACE-inhibitors may be circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. Serum enalaprilat levels 100–and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril, respectively.

Treatment:
The recommended treatment of overdose is intravenous infusion of saline solution. If hypotension occurs, the patients should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamine may also be considered. If the tablets were ingested is recently, measures to eliminate enalapril maleate should be taken (e.g. vomiting, gastric lavage, administration of adsorbents or sodium sulphate). Enalaprilat can be removed from the circulation by haemodialysis (see 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine should be continuously monitored.

[...]
In the post-marketing experience, some cases of intentional overdose requiring hospitalization were reported with administration of enalapril/lercanidipine at doses from 100 up to 1000 mg.
each. The reported symptoms (blood pressure systolic decreased, bradycardia, restlessness, somnolence and flank pain) could also be due to the concomitant administration of high doses of other drugs (e.g. beta-blockers).

**Symptoms of overdose with enalapril and lercanidipine alone:**

The most prominent features of overdose reported with enalapril to date are marked hypotension (beginning some six hours after ingestion of the tablets), concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdose of ACE-inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. Serum enalaprilat levels 100- and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril respectively.

As with other dihydropyridines, overdose with lercanidipine might be expected to cause excessive peripheral vasodilatation with marked hypotension and reflex tachycardia.

**Treatment of cases of overdose with enalapril and lercanidipine alone:**

The recommended treatment of overdosage with enalapril is intravenous infusion of saline solution. If hypotension occurs, the patients should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If the tablets were ingested recently, measures to eliminate enalapril maleate should be taken (e.g. vomiting, gastric lavage, administration of absorbents or sodium sulfate). Enalaprilat can be removed from the circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine should be continuously monitored.

With lercanidipine, in the case of severe hypotension, bradycardia and unconsciousness, cardiovascular support can be helpful, with intravenous atropine to counteract the bradycardia. In view of the prolonged pharmacological action of lercanidipine, the cardiovascular status of patients who have taken an overdose must be monitored for at least 24 hours. There is no information about the value of dialysis. Since the drug is highly lipophilic, it is very unlikely that plasma levels will be indicative of the duration of the risk phase. Dialysis may not be effective.

**5. Pharmacological Properies**

**5.1 Pharmacodynamic properties**

Enalapril

[...]

Decreases in albuminuria and urinary excretion of IgG and total protein were seen after ingestion of enalapril in short-term clinical studies in diabetic and non-diabetic patients with renal disease.
In short-term clinical studies in diabetic and non-diabetic patients with renal disease, decreases in albuminuria and urinary excretion of IgG and total urinary protein were seen after the administration of enalapril.

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.

Enalapril/Lercanidipine
The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

[...]

In a pivotal phase III, double blind, add-on clinical trial conducted in 327 non responders to enalapril 20 mg (defined as SDBP 95-114 and SSBP 140-189 mmHg), patients on enalapril 20 mg/lercanidipine 10 mg achieved a significantly greater reduction in trough SSBP compared with those on monotherapy (-9.8 vs -6.7 mmHg, p=0.013) and in trough SDBP (-9.2 vs -7.5 mmHg, p=0.015). Responder rates were not significantly higher with combination therapy than with monotherapy (53% vs 43%, p=0.076 for SDBP and 41% vs 33%, p=0.116 for SSBP) and a not significantly higher percentage of patients on combination therapy experienced normalization of SDBP (48% vs. 37%, p=0.055) and of SSBP (33% vs 28%, p=0.325) compared with patients on monotherapy. No comparative data exist with a combination enalapril 20 mg/lercanidipine 20 mg.

In a placebo and active-controlled randomized double blind study with a factorial design conducted on 1,039 patients with moderate hypertension (defined as office SDBP 100-109 mmHg, SSBP < 180 mmHg and home DBP ≥ 85 mmHg), patients on enalapril 20mg/lercanidipine 20 mg had a significantly greater reductions in office and home SDBP and SSBP compared with placebo (P<0.001). Clinically relevant differences in the change from baseline in office SDBP at trough were observed between combination therapy 20mg/20mg (−15.2 mmHg, n=113) in comparison with enalapril 20mg (−11.3 mmHg, P=0.004, n=113) or lercanidipine 20mg alone (−13.0 mmHg, P=0.092, n=113). Similarly, clinically relevant
differences were observed in the change from baseline in office SSBP at trough between combination therapy 20mg/20mg (−19.2 mmHg) compared with lercanidipine 20mg (−13.0 mmHg, \( P=0.002 \)) or enalapril 20mg alone (−15.3 mmHg, \( P=0.055 \)). Clinically relevant differences were also observed in home SBP and DBP. A significant increase in the responder rates for SDBP (75%) and SSBP (71%) was observed with combination therapy 20mg/20mg over placebo (\( P<0.001 \)) and both monotherapies (\( P<0.01 \)). Normalization of blood pressure was achieved by a higher percentage of patients treated with combination therapy 20mg/20mg (42%) than with placebo (22%).

5.2 Pharmacokinetic properties

[...]

**Distribution**

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin-converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril maleate. The effective half-life for accumulation of enalapril following concentrations of enalaprilat was reached after four days of treatment. Peak serum concentrations of enalaprilat occur about 4 hours after an oral dose of enalapril maleate. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours. In subjects with normal renal function, steady-state serum concentrations of enalaprilat was reached after four days of treatment. [...]

5.3 Preclinical safety data

[...]

**Lercanidipine**

The relevant effects which have been observed in long term studies in rats and dogs were related, directly or indirectly, to the known effects of high doses of Ca-antagonist, predominantly reflecting exaggerated pharmacodynamic activity.

Lercanidipine showed no genotoxicity or evidence of carcinogenic hazard.

Non–clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

[...]
העלון לצרכן בヶ月 טובש 2015, העדכוןyny ב-2015, העדכון
הינו בסעיפים הבאים:

1. הקדמה

chodי קומבזוזודיפ לאטרופל בטולים בנגד לחם ומתח ליגי.
chodי קומבר אף מעשה לטיפול ראשוני בתרופה של לחם.

2. ממתיロー לשהות בטכחה?

- הינך בהריון, למעט 3-3 החודשים (עדכן לה בגין דיוויד קומבזוזודיפ זמינות בبعثתのはריאן הרשיאנוס
- הינך סובל מסוכרת או פסי איבוד הסיכון לאי החום, ספיקת חלב מעורב מברשת שהחרית דם
- הינך סובל ממחלות הלב הבאות: אי ספיקת לבר של המטרה, חוסמת הזרמה מהחדר השמאלי
- הינך סובל מליקוי חמור בתפקוד הכבד או הכליות, או שאתה עובד דיליזה
- הינך סובל ממספר תרופות נזכרות.ab
- הינך מ𝗴ב מCollapse מחמצים, הקצרים או הכליות, בין אם ההובלת דיליזה
- הינך סובל ממספר תרופות או בטכחה על רקע לא ידוע
- יש לך נטייה תורשתית להתנפחות רקמות או אם אתה סובל מהתנפחות רקמות על רקע לא ידוע
- אתה אוכל כימיה או שותה מיץ כימיה
- יש לדווח לרופא המטפל על נטילת תרופה זו לפני: ניתוח או הרדמה (לヵון דנטה), לטיפול לדיליזה, לטיפול בתרופה של בריאות
- הסבר להfprintfה, בריאות ותרופה. דוברגת
- יש לדווח על נדיבות לעכ psy, ישים.
- אם ברזים טיפולי את התכיפה, עכ psy, ישים, על כל אוכם משליש

יאו לשהות בטכחה משליש ליהיו הספרות לنبي התכיפה המסייעית.
•Eat moderate amounts of food (with astronauts and staff, or at home) and maintain a balance between eating and drinking.

• Eat breakfast, lunch, and dinner. Avoid eating too much at one time.

• Chew your food slowly and fully. This helps your body break down the food and absorb nutrients more efficiently.

• Avoid eating foods that are difficult to swallow, such as those that stick to your teeth or get stuck in your throat.

• Avoid taking additional supplements or medications, especially those that can cause digestive problems.

• If you have difficulty swallowing, consult a doctor to determine the cause and appropriate treatment.

• Avoid eating spicy foods, citrus fruits, or other acidic foods that can irritate your throat.

• If you experience persistent swallowing difficulties, consult a doctor.

• Avoid eating foods that are difficult to chew or swallow, such as those that stick to your teeth or get stuck in your throat.

• Avoid taking additional supplements or medications, especially those that can cause digestive problems.

• If you have difficulty swallowing, consult a doctor to determine the cause and appropriate treatment.

• Avoid eating spicy foods, citrus fruits, or other acidic foods that can irritate your throat.

• If you experience persistent swallowing difficulties, consult a doctor.

[^]
אם הינך מטופל בתרופות לסוכרת, возможно היפוגליקמיה (רמת סוכר נמוכה בדם)ぼｽ诊疗 즏osis 등, בلوح של וזודיפ קומבו עם תרופות אלו, בחודש cerco לטיפול.

חמשי בטא

תרופות לטיפול בלחץ דם ובבעיות לב.

ייתכן והרופא שלך יצטרך לשנות את המינון שלך או לנקוט באמצעי זהירות אחרים אם אתה לוקח חוסמי רצפטור אנגיוטנסין 2 או אליסקיין רاك ספיפת אי抑え "סתורט" ו"אי לטישטמש בתרופה".

3.דיאדה השמשת בתרופה:

على לברד לו הרופה או הרוקח או אלא בונה. מבוית קומבו לא מומלט לטיפול בדם ומעבר של משותפ.

ליג 18.

4.תופעות לוואי

יש להפסיק את הטיפול בתרופה ולפנות לרופא ואם מופיעות התופעות הבאות:

• התנפחות של הפנים, גפיים, שפתיים, רקמות ריריות, לשון,innamon.
• קצער נשימה.
• הכהבה של העור ושל רקמות ריריות.
• חום, התנפחות קשרי לימפה, או דלקת של הגרון.
• יש לפנות לרופא מיד אם מופיעות תגובות אלרגיות}"אתחלת הטיפול בתרופה, היא עלולה להרגיש חלש או מסוחררו או בטיסטש ראייה. זה קורה בעקבות נפילה פרוטומית בלחץ הדם שלך. בקרה זה, יש לשכוב. אם אתה דעי, ספור לזרוז שולך. פתואומיות כלוח מדבר שולך. בקטריה זה, יש לשכוב. אם אתה דעי, ספור לזרוז שולך.

תופעות לוואי ספיפות בתופעת 1-10 מֶשֶׁתמשות מֶתָכ 100:

כבר ראה, עסופן, סחורה, זיכרון, שעון בuggestionsו, ואחרים...
The first table states:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain, shortness of breath, dizziness</td>
<td>1-10 of 1000</td>
</tr>
<tr>
<td>Headache, chest pain, lightheadedness, sweating</td>
<td>10,000</td>
</tr>
</tbody>
</table>

The second table states:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia, low blood pressure, fast or irregular heartbeat</td>
<td>1-10 of 1000</td>
</tr>
<tr>
<td>Tiredness, weakness, nausea, vomiting</td>
<td>10,000</td>
</tr>
</tbody>
</table>

The third table states:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low blood pressure, chest pain, fatigue, joint pain, cold hands</td>
<td>1-10 of 1000</td>
</tr>
<tr>
<td>Tiredness, weakness, nausea, vomiting</td>
<td>10,000</td>
</tr>
</tbody>
</table>

The fourth table states:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue, weakness, nausea, vomiting</td>
<td>1-10 of 1000</td>
</tr>
<tr>
<td>Tiredness, weakness, nausea, vomiting</td>
<td>10,000</td>
</tr>
</tbody>
</table>
אנמיה (כולל אנמיה אפלסטית והובילית), רמות נמוכות של סוכר או נתרן בדם (1-10 מlesaiים ממון ב-10,000 ממנה) הופכים לבקל. לרמות גבוהות של אוריאה בדם (0.001), תופעות לוואי נדירות תופעות שמופיעות ב-1-10 מהמשתמשים ממון ב-1,000: (1) קת חזה קיימת במטופלים עם תנועה, הם יכולים לחוות עלייה בתדירות, בדוקות או בחומרה של ההתקפים בעקבות שימוש במשפחה של תרופות שא oblivית לרקנידיפין.

.Uלרקנידיפין

1. נפיחות של המעיים (אנגיוא噴) (1) הקאה, צרבת, כאבי שרירים. נפיחות של המעיים (אנגיואренוס). (2) קורעה או בעיות שינה, ניסיון של קורעה, מקומים שונים, רמות גבוהות של בילירובין בדם (0.001), תופעות לוואי נדירות非常喜欢 תופעות שמופיעות ב-1-10 מהמשתמשים ממון ב-10,000: (1) קת חזה קיימת במטופלים עם תנועה, הם יכולים לחוות עלייה בתדירות, בדוקות או בחומרה של ההתקפים בעקבות שימוש במשפחה של תרופות שא oblivית לרקנידיפין.

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