יוני 2013

VASODIP COMBO 10, VASODIP COMBO 20

צוות רפואי נכבד,

חברת דקסל פארמה מבקשת להודיעכם על עדכון בעלונים לצרכן ולרופא של התכשירים:

VASOIP COMBO 10 , VASODIP COMBO 20

העלונים לצרכן ולרופא נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס

ע"י פנייה לבעל הרישום: דקסל בע"מ, רח' דקסל 1, אור – עקיבא 3060000, ישראל, טל':

04-6364000.

הרכב:

VASODIP COMBO 10:

LERCANIDIPINE HYDROCHLORIDE	**10 mg**
ENALAPRIL MALEATE	**10 mg**

VASODIP COMBO 20:

LERCANIDIPINE HYDROCHLORIDE	**10 mg**
ENALAPRIL MALEATE	**20 mg**

התוויה מאושרת:

VASODIP COMBO 10:

Treatment of essential hypertension in whose blood pressure cannot be adequately controlled under lercanidipine monotherapy.

VASODIP COMBO 20:

Treatment of essential hypertension in patients whose blood pressure cannot be adequately controlled under enalapril monotherapy.

<u>עלון לצרכן</u>

קבוצה תרפויטית:
אנלפריל שייך לקבוצת מעכבי אנזים המהפך אנגיוטנסין (ACE inhibitor).
לרקנידיפין שייך לקבוצת חוסמי תעלות סידן.
~~אנלפריל ולרקנידיפין משמשים לטיפול ביתר לחץ דם.~~
...
מתי אין להשתמש בתכשיר?

אם ידועה רגישות לאחד ממרכיבי התרופה או לתרופות אחרות מאותן קבוצות תרפויטיות (ראה/י לעיל).
אם הינך בהריון ~~או מניקה~~, מעל 3 חודשים (ראי סעיף אזהרות).
אם הינך סובל/ת ממחלות הלב הבאות: אי ספיקת לב ~~מוגדש~~ (congestive heart failure) ולא מטופלת, חסימת זרימת דם מהחדר השמאלי של הלב כולל היצרות של אבי העורקים, תעוקת לב לא יציבה (~~תעוקה~~ במנוחה או שגדלה בהדרגה), התקף לב במהלך החודש האחרון.
אם הינך סובל/ת מליקוי חמור בתפקוד הכבד או הכליות, או שאת/ה עובר/ת דיאליזה.
אם הינך נוטל/ת תרופות נגד פטריות (כגון קטוקונאזול או איטרקונאזול), אנטביוטיקות ממשפחת המקרולידים(כגון אריתרומיצין), תרופות נגד וירוסים (כגון ריטונביר), ציקלוספורין.
אם סבלת מאנגיואדמה (בצקת של הפנים, השפתיים, הלשון ו/או הגרון, הידיים והרגליים) עקב סיבה תורשתית או בעקבות שימוש בתרופה מקבוצת מעכבי אנזים המהפך אנגיוטנסין (ACE-inhibitor).
...

אין להשתמש בתרופה מבלי להיוועץ ברופא לפני התחלת הטיפול:
אם הינך סובל/ת ~~או סבלת בעבר~~ ממחלת לב או ליקוי בזרימת הדם (כולל במוח), מבעיות בכליות ~~(כולל חולים העוברים דיאליזה ומושתלי כליה)~~, מעליה ברמת אנזימי הכבד או צהבת, סוכרת, ממחלות רקמת חיבור עם מעורבות של כלי דם, אם ספירת תאי הדם הלבנים שלך נמוכה (לויקופניה ,אגרנולוציטוזיס),מצב העלול לגרום לעליה בסיכון לפתח זיהומים, אם הינך נוטל אלופורינול (לטיפול בשיגדון), פרוקאינאמיד (לטיפול בהפרעות קצב בלב) או ליתיום (לטיפול במצבים נפשיים מסוימים)
אם את/ה בסיכון לפתח רמות גבוהות של אשלגן בדם, אם הינך סובל/ת או מפתח/ת שיעול יבש ומתמיד, אם הירידה בלחץ הדם אינה מספקת וקשורה במוצא האתני (בעיקר במטופלים בעלי עור כהה). אם את חושבת שאת בהריון או עשויה להיכנס להריון או מניקה (ראי סעיף אזהרות).
...
הריון: וזודיפ קומבו אינו מומלץ לשימוש בתחילת ההיריון, ואסור לשימוש בהריון מתקדם (מעל 3 חודשים), כיוון שהוא עלול לגרום לנזק חמור בעובר.
הנקה: הנקת תינוקות בשבועות הראשונים לאחר הלידה ובעיקר תינוקות שנולדו לפני הזמן, אינה מומלצת בזמן נטילת **וזודיפ קומבו**. יש להיוועץ עם הרופא לגבי הנקת תינוקות בוגרים יותר.
תגובות בין תרופתיות:
אם הינך נוטל/ת תרופה נוספת, או אם סיימת זה עתה טיפול בתרופה אחרת, כולל תרופות ללא מרשם, עליך לדווח לרופא המטפל כדי למנוע סיכונים או אי-יעילות הנובעים מתגובות

בין תרופתיות, במיוחד לגבי תרופות מהקבוצות הבאות: ציקלוספורין (לדיכוי מערכת החיסון), אלופורינול (לטיפול בשיגדון), פרוקאינאמיד (לטיפול בהפרעות קצב בלב), תרופות לבליעה נגד פטריות (כגון קטוקונאזול ~~או~~ ואיטרקונאזול), תרופות נגד וירוסים (כגון ריטונביר), אנטיביוטיקות ממשפחת מקרולידים (כגון אריתרומיצין), סימטידין (~~למשל~~ לכיב קיבה במינון הגבוה מ-800 מ"ג ליום), משתנים (כגון הידרוכלורותיאזיד, פורוזמיד, אמילוריד, אינדפמיד, ספירונולקטון), תרופות להורדת לחץ דם, תרופות להרחבת כלי דם (כגון ניטרוגליצרין, איזוסורביד או ניטרטים אורגנים אחרים, חומרי הרדמה ואלחוש), דיגוקסין, תרופות להסדרת קצב הלב (כגון אמיודרון, קווינידין), תרופות נגד דיכאון, תרופות אנטי פסיכוטיות, תרופות נוגדות דלקת שאינן סטרואידיות - NSAIDs (כגון איבופרופן, נפרוקסן, אינדומתצין, אספירין), פראצטמול, תרופות המשפיעות על הרחבה או היצרות של כלי דם (כגון נוראדרנלין, איזופרנלין, דופאמין, סלבוטמול), תרופות נגד עוויתות (כגון פניטואין, קרבמזפין), באקלופן, ריפאמפיצין (לטיפול בשחפת), תרופות המכילות אשלגן או תוספי אשלגן, אנטי-היסטמינים.

...

תופעות לוואי המופיעות לעיתים קרובות

כאב ראש, עייפות, סחרחורת, חולשה, דיכאון, שיעול, בחילה, שלשול, כאב בטן, שינויים בחוש הטעם, פריחה או אדמומיות ותחושת חום בעור, הסמקה/אדמומיות של הפנים, קצב לב מהיר, קצב לב לא סדיר, התקף לב או שבץ, כאב או לחץ בחזה, ירידה מוגזמת בלחץ דם גם כאשר נעמדים, אובדן הכרה לזמן קצר, ~~נזלת~~,הפרעות בראייה, נפיחות בקרסוליים. עליה ברמת אשלגן וקריאטינין בדם. ~~יש לפנות לרופא אם תופעות אלו נמשכות או מטרידות.~~

תופעות לוואי המופיעות לעיתים רחוקות

אנמיה, רמות נמוכות מאד של סוכר בדם, בלבול, נמנום, חוסר שינה, עצבנות, תחושת נימול או עקצוץ, דפיקות לב, הפרשות מהאף, כאב גרון וצרידות, צפצופים בנשימה, אסטמה, חסימת מעיים, דלקת בלבלב, כיב בקיבה, הקאות, קשיי עיכול, עצירות, אובדן תיאבון, גירוי בקיבה, יובש בפה, הזעה מוגברת, גירוד, חרלת, אובדן שיער, בעיות בכליות, אין אונות, התכווציות שרירים, צלצולים באוזניים, תחושת חולי. עלייה ברמת אוריאה בדם, ירידה ברמת נתרן בדם, ~~בצקת פריפרית (בעיקר בהתחלת הטיפול), נטייה לזיהומים, הפרעות בזרימת דם לידיים ולרגליים, עוויות הסימפונות.~~

תופעות לוואי המופיעות לעיתים נדירות מאד

ירידה בספירת תאי דם מסוימים, שינויים בתוצאות מעבדה, ירידה בתפקוד מח העצם, מחלות אוטואימוניות, שינויים בחלומות, הפרעות בשינה, כפות ידיים ורגליים קרות, משיכה באף, דלקת ריאות, דלקת בפה עם היווצרות כיבים, דלקת בלשון, כשל כבד, דלקת בכבד, פריחות חמורות בעור, מיעוט או ריבוי בהטלת שתן, הגדלה של החזה בגברים.
ייתכן מצב בו יופיעו חלק או כל התופעות הבאות: חום, דלקת של ריריות, דלקת של כלי הדם, כאב או דלקת בשרירים או במפרקים ושינויים בתוצאות בדיקות מעבדה; פריחה בעור, רגישות לאור והופעת תגובות עוריות אחרות.

תופעות לוואי נוספות

עיבוי החניכיים, נפיחות במעיים.
אם אחת מתופעות הלוואי מחמירה, ~~בכל מקרה שבו~~ או אם הינך מרגיש/ה תופעות לוואי שלא צוינו בעלון זה, ~~או אם חל שינוי בהרגשתך הכללית~~ עליך להתייעץ עם הרופא~~מיד~~.

מינון:

...

אם שכחת ליטול תרופה זו בזמן הקצוב יש ליטול אותה מיד כשנזכרת, אלא אם מועד הנטילה הבאה קרוב. בשום אופן אין ליטול שתי מנות ~~ביחד~~ באותו היום!

עלון לרופא

VASODIP COMBO

SUMMARY OF PRODUCT CHARACTERISTICS

...

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

…

Excipients:
Vasodip Combo 10: one film-coated tablet contains 102.0 mg of lactose monohydrate.
Vasodip Combo 20: one film-coated tablet contains 92.0 mg of lactose monohydrate.
For a full list of excipients, see section 6.1.

…

4.1 Therapeutic indications

…

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

4.2 Posology and method of administration

...

Individual dose titration with the components can be recommended. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

The recommended dose is 1 tablet taken once daily at least 15 minutes before a meal. Treatment should be preferably administered in the morning. This product should not be administered with grapefruit juice (see section 4.3 and 4.5).

….

4.3 Contraindications

...

- ~~during~~ second and third trimesters of pregnancy ~~and lactation~~ (see 4.4 and 4.6)
- ~~in women of child-bearing potential unless effective means of contraception are used.~~
- left ventricular outflow obstruction, including aortic stenosis

…

- severe renal impairment(creatinine clearance < 30 ml/min), including patients undergoing haemodialysis

…

4.4 Special warnings and special precautions for use

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

…
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)

~~Haemodialysis patients~~
~~Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. "AN 69") and treated concomitantly with an ACE inhibitor. In these patients a different type of dialysis membrane or a different class of antihypertensive agent should be used.~~
…

~~Vasodip Combo is contraindicated in patients with severe impairment of liver function (see 4.2).~~

Pregnancy
Vasodip Combo is not recommended during pregnancy.

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

The use of lercanidipine is also not recommended during pregnancy or in women planning to become pregnant (see 4.6)

Lactation
The use of Vasodip Combo is not recommended during lactation (see 4.6).

…
4.5 Interaction with other medicinal products and other forms of interaction
…

Lercanidipine
Contraindicated combinations
Inhibitors of CYP3A4
Since lercanidipine is metabolised by the enzyme CYP3A4, simultaneously administered inhibitors and inducers of CYP3A4 may interact with the metabolism and excretion of lercanidipine.
The combination of lercanidipine and strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin) is contraindicated (see 4.3).

An interaction study with ketoconazole, a strong inhibitor of CYP3A4, showed a marked rise in plasma levels of lercanidipine (a 15-fold increase in area under the drug concentration-time curve [AUC] and an 8-fold increase in C_{max} of the eutomer S-lercanidipine).
…

Combinations requiring precautions for use
Alcohol
Alcohol should be avoided since it may potentiate the effect of vasodilator antihypertensives (see 4.4).
…
Combinations to be taken into account

Midazolam
In elderly volunteers the concurrent administration of oral midazolam 20 mg enhanced the absorption of lercanidipine (by about 40%) and decreased its rate of absorption (t_{max} was delayed from 1.75 to 3 hours). No changes in midazolam concentrations occurred.

Metoprolol
When lercanidipine was co-administered with metoprolol - a ß-blocker predominantly eliminated by the liver - the bioavailability of metoprolol was unchanged, whereas the bioavailability of lercanidipine was reduced by 50%. This effect may be due to the reduction in hepatic blood flow caused by ß-blockers and hence might also occur with other preparations of this class of drug. Nevertheless, lercanidipine can be safely used at the same time as blockers of β-adrenergic receptors. ~~Enalapril can be used safely together with beta blockers.~~
…

Enalapril maleate
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.

Not recommended combinations
Potassium-sparing diuretics and 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 demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium (see 4.4).
…

Estramustine:

Risk of increased adverse effects such as angioneurotic oedema (angioedema) (see 4.4).

Combinations requiring precautions for use

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE-inhibitors and antidiabetic drugs (insulin, oral antidiabetics) may cause an increased blood glucose-lowering effect, with risk of hypoglycaemia. These cases are apparently more likely to occur in the first weeks of combined treatment and in patients with renal impairment.

…

Baclofen

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

Ciclosporin

Ciclosporin increases the risk of hyperkalaemia with ACE inhibitors.

Alcohol

Alcohol enhances the hypotensive effect with ACE inhibitors.

Combinations to be taken into account

Amifostine

Increased antihypertensive effect.

…

Corticosteroids, tetracosactide (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

Antiacids 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.

…

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including enalapril.

4.6 Pregnancy and lactation

~~Vasodip Combo is contraindicated during pregnancy and lactation.~~

Pregnancy

~~Data on the use of lercanidipine do not suggest a teratogenic effect in rats and rabbits. There was no influence on the reproduction rate in rats. There is no clinical data available on the use of lercanidipine during pregnancy and lactation. In animal studies other dihydropyridine compounds showed teratogenic effects. Women of childbearing potential must not be treated with lercanidipine, unless a safe method of contraception is used.~~

~~Controlled clinical studies with ACE inhibitors were not carried out in humans. However, in a limited number of cases where pregnant women were exposed during the 1st trimester showed no foetal malformation corresponding to the toxic effects described below.~~

~~It is known that long-term use of enalapril in humans during the 2nd and 3rd trimester has a toxic effect on the foetus (worsening of renal function, oligohydramnios, skull ossification retardation) and on the new-born child (renal failure, hypotension, hyperkalaemia) (see also 5.3).~~

~~Should exposure to Vasodip Combo have occurred after the first trimester of pregnancy, ultrasound check of the kidneys and the skull is recommended.~~

~~Infants, whose mothers have used Vasodip Combo, should be carefully monitored with regard to hypotension, oliguria and hyperkalaemia. Enalapril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.~~

For enalapril

The use of ACE inhibitors (enalapril) is not recommended during the first trimester of pregnancy (see 4.4).The use of ACE inhibitors (enalapril) is contra-indicated during the second and third trimesters of pregnancy (see 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 anti-hypertensive 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 trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See 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 4.3 and 4.4).

For lercanidipine

Animal studies with lercanidipine have not shown teratogenic effects, but these have been observed with other dihydropyridine compounds.
No clinical data on exposed pregnancies are available for lercanidipine, therefore its use is not recommended during pregnancy or in women planning to become pregnant.

For enalapril and lercanidipine in association
Consequently, the use of Vasodip Combo is not recommended during the first trimester of pregnancy and it is contraindicated from the second trimester of pregnancy onwards.

Lactation
~~In view of the high lipophilicity of lercanidipine, excretion into breast milk may be expected.~~
~~Enalapril and enalaprilate are excreted into human breast milk. Their effect on the breastfed infant, however, has not been investigated.~~
For enalapril
Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see 5.2). Although these concentrations seem to be clinically irrelevant, the use of Vasodip Combo in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of Vasodip Combo in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

For lercanidipine
The excretion of lercanidipine in human milk is unknown.

For enalapril and lercanidipine in association
Consequently, the use of Vasodip Combo is not recommended during lactation.
…

4.8 Undesirable effects

The undesirable effects of the combined preparation are similar to those that have been observed with one or other of the constituents when given alone.

The MedDRA system organ class and frequency convention has been followed: very common (> 1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥ 1/10000 to < 1/1000), very rare (<1/10000) not known (cannot be estimated from the available data).

In controlled clinical trials using the combination lercanidipine hydrochloride 10 mg/ enalapril maleate 10 mg and including 329 patients, undesirable effect were reported as shown in the following table.
~~See table~~

Adverse drug reactions observed with Vasodip Combo 10:

System organ class	**Frequency**	
	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)
Immune system disorders		Hypersensitivity*

Nervous system disorders	Dizziness	Headache ~~Unconsciousness*~~
Ear and labyrinth disorders	Vertigo, including vertigo positional	
Cardiac disorders		Palpitations Tachycardia*
Vascular disorders		Hypotension* Circulatory collapse*
Respiratory, thoracic and mediastinal disorders	Cough	Dry throat*
Gastrointestinal disorders		Abdominal pain upper* Nausea*
Skin and subcutaneous tissue disorders		Dermatitis* Erythema* Lip oedema* Urticaria*
Musculoskeletal and connective tissue disorders		Arthralgia*
Renal and urinary disorders		Polyuria* Pollakiuria*
Reproductive system and breast disorders		Erectile dysfunction*
General disorders and administration site conditions		Fatigue Asthenia*
Investigations		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:

System organ class	**Frequency**	
	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)
Immune system disorders		Angioedema*
Blood and lymphatic system disorders		Thrombocytopenia

Metabolism and nutrition disorders		Hypertriglyceridaemia*
Psychiatric disorders		Anxiety*
Nervous system disorders	Headache Dizziness (including dizziness postural)	
Cardiac disorders		Palpitations
Vascular disorders	Flushing	Hypotension*
Respiratory, thoracic and mediastinal disorders	Cough	Pharyngolaryngeal pain*
Gastrointestinal disorders		Abdominal pain Constipation* Dyspepsia* Nausea* Tongue disorder*
Skin and subcutaneous tissue disorders		Erythema* Rash*
Musculoskeletal and connective tissue disorders		Arthralgia*
Renal and urinary disorders		Nocturia*
General disorders and administration site conditions	Oedema peripheral	Asthenia Fatigue Feeling hot* ~~Weakness*~~
Investigations		ALT increased AST increased
Note: *in 1 patient only.		

Additional information on the individual components.

Lercanidipine alone
Adverse reactions occurred in approximately 1.8% of patients treated.

~~The incidence of adverse drug effects which were considered to be at least possibly causally related to the treatment is given below, grouped by WHO-ART classification system and ranked by frequency (uncommon, rare).~~

…

Immune system disorders
Very rare: hypersensitivity

…
Very rare: syncope

…

Blood and lymphatic system disorders:
Uncommon: anaemia (including aplastic and haemolytic forms)

Rare: neutropenia, thrombocytopenia, agranulocytosis, ~~myelosuppression~~ bone marrow failure, pancytopenia, lymphadenopathy.

Immune system disorders:
Common: hypersensitivity, angioedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx have been reported (see 4.4)
Rare: autoimmune disorder

Metabolism and nutrition disorders:
Uncommon: hypoglycaemia (see 4.4), anorexia
...

Ear and labyrinth disorder:
Uncommon: vertigo, tinnitus

…
Vascular disorders:
Common: hypotension, syncope, cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see 4.4)
Uncommon: flushing, orthostatic hypotension
Rare: Raynaud's phenomenon

...

Gastrointestinal disorders:
..
Uncommon: ileus, pancreatitis, vomiting, dyspepsia, constipation, ~~loss of appetite,~~ stomach discomfort, dry mouth, peptic ulcer
Rare: stomatitis, aphthous stomatitis, glossitis
Very rare: intestinal angioedema
...

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

Musculoskeletal and connective tissue disorders:
Uncommon: muscle spasms

...

General disorders and administration site conditions:
..
Uncommon: malaise~~, 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.

...

Experience with lercanidipine overdose
Symptoms:
…
In post-marketing experience, ~~two~~ 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 ~~of~~ respectively in: gastric lavage; high-dose catecholamines, furosemide, digitalis and parenteral plasma expanders; activated charchoal, 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.
...

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

…
In a pivotal phase III, double blind, add-on clinical trial conducted in 342 non responders to lercanidipine 10 mg (defined as SDBP 95-114 and SSBP 140-189 mmHg), the reduction in trough SSBP was 5.4 mmHg greater with the combination enalapril 10 mg/lercanidipine 10 mg than with lercanidipine 10 mg alone after 12 weeks of double-blind treatment (-7.7 mmHg vs -2.3 mmHg, $p<0.001$). Also the reduction in trough SDBP was 2.8 mmHg greater with the combination as compared to the monotherapy (-7.1 mmHg vs -4.3 mmHg, $p<0.001$). Responder rates resulted significantly higher with combination therapy than with monotherapy: 41% vs 24% ($p< 0.001$) for SSBP and 35% vs 24% ($p=0.032$) for SDBP. A significantly higher percentage of patients on combination treatment experienced normalization of SSBP (39% vs 22%, $p<0.001$) and of SDBP (29% vs 19%, $p=0.023$) compared with patients on monotherapy. In the open-label long term follow-up phase of this study a titration to the combination enalapril 20 mg/lercanidipine 10 mg was allowed if BP remained >140/90 mmHg: titration occurred in 133/221 patients and SDBP normalized after titration in 1/3 of these cases.

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 clinical phase III studies the combination preparation achieved an additive effect in patients in whom monotherapy with lercanidipine or enalapril did not provide adequate control and blood pressure was lowered to a greater extent than under the individual components alone.~~

...

5.2 Pharmacokinetic properties

...

Distribution

~~The effective half-life for accumulation of enalaprilate after repeated oral administration is 11 hours.~~ 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. Over the range of concentrations which are therapeutically relevant, enalapril binding to human plasma proteins does not exceed 60%.

...

Renal impairment ~~of kidney function~~

The exposure of enalapril and enalaprilat is increased in patients with renal insufficiency. In patients with mild to moderate renal insufficiency (creatinine clearance 40-60 ml/min), the steady state AUC of enalaprilat was approximately two-fold higher than in patients with normal renal function after administration of 5 mg once daily. In severe renal impairment (creatinine clearance ≤ 30 ml/min), the AUC was increased approximately 8-fold. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency and time to steady state is delayed (see section 4.2).
Enalaprilate may be removed from the general circulation by haemodialysis. The dialisys clearance is 62 ml/min.

Lactation

After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7µg/L (range 0.54 to 5.9 µg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7µg/L (range 1.2 to 2.3µg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively breastfed infant would be about 0.16% of the maternal weight-adjusted dosage. A woman who had been taking oral enalapril 10 mg daily for 11 months had peak enalapril milk levels of 2 µg/L 4 hours after a dose and peak enalaprilat levels of 0.75 µg/L about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24 hour period was 1.44µg/L and 0.63 µg/L of milk respectively. Enalaprilat milk levels were undetectable

(<0.2µg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10mg in two mothers; enalapril levels were not determined.

5.3 Preclinical safety data

Enalapril : lercanidipine combination
Potential toxicity of the fixed combination of enalapril and lercanidipine was studied in rats after oral administration for up to 3 months and in two genotoxicity tests. The combination did not alter the toxicological profile of the two individual components.

~~No further preclinical safety studies were performed with Vasodip Combo.~~ The following data exist for the two individual components, enalapril and lercanidipine.

Lercanidipine
~~Safety pharmacological studies in animals have shown no effects on the autonomic nervous system, the central nervous system or on gastrointestinal function at antihypertensive doses.~~
...
Lercanidipine showed no genotoxicity or evidence of carcinogenic hazard.
Treatment with lercanidipine had no effect on fertility or general reproductive performance in rats, but at high doses induced pre- and post- implantation losses and delay in fetal development. There was no evidence of any teratogenicity effect in rats and rabbits, but other dihydropyridines have been found to be teratogenic in animals.
Lercanidipine induced dystocia when administered at high dose (12 mg/kg/day) during labour.
The distribution of lercanidipine and/or its metabolites in pregnant animals and their excretion in breast milk have not been investigated.
~~Metabolites have not been evaluated separately in toxicity studies.~~

Enalapril
...
ACE-inhibitors, as a class, have been shown to induce adverse effects on the late fetal development, resulting in fetal death and congenital effects, in particular affecting the skull. Fetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to a direct action of ACE inhibitors on the fetal renin angiotensin system and partly due to ischemia resulting from maternal hypotension and decreases in fetal-placental blood flow and oxygen/nutrients delivery to the fetus.

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6.4 Instructions for use and handling and disposal

~~No special requirements.~~ Any unused product or waste material should be disposed of in accordance with local requirements.
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